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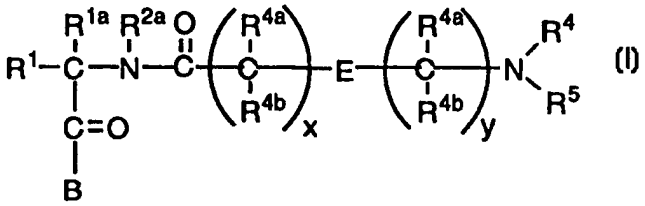
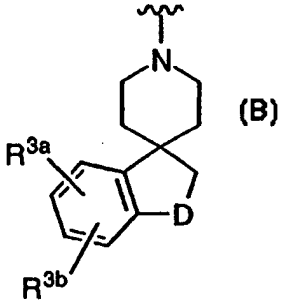
(54) Title: PIPERIDINES, PYRROLIDINES AND HEXAHYDRO-1H-AZEPINES PROMOTE RELEASE OF GROWTH HORMONE

(57) Abstract

The present invention is directed to certain piperidines, pyrrolidines, and hexahydro-1H-azepines of general structural formula (I) wherein B is selected from (A) and (B) and R^1, R^{1a}, R^{2a}, R^{3a}, R^{3b}, R^4, R^{4a}, R^{4b}, R^5, D, E, X, Y, n, x and y are as defined herein. These compounds promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing such compounds as the active ingredient thereof are also disclosed.



(I)



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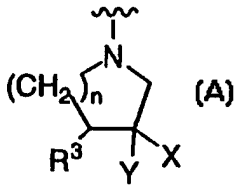

(A)

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TITLE OF THE INVENTION

PIPERIDINES, PYRROLIDINES AND HEXAHYDRO-1H-AZEPINES PROMOTE RELEASE OF GROWTH HORMONE

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body: (1) Increased rate of protein synthesis in all cells of the body; (2) Decreased rate of carbohydrate utilization in cells of the body; (3) Increased mobilization of free fatty acids and use of fatty acids for energy. A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which

must be given by injection or by a nasal spray. Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. Non peptidal growth hormone secretagogues are disclosed in e.g., U.S. Patent Nos 5,206,235, 5,283,241, 5,284,841, 5,310,737, 5,317,017, 5,374,721, 5,430,144, 5,434,261, 5,438,136, 5,492,916, 5,494,919, 5,494,920, and 5,536,716. Other growth hormone secretagogues are disclosed e.g., in PCT Patent Publications WO 94/13696, WO 94/19367, WO 95/03289, WO 95/03290, WO 95/09633, WO 95/11029, WO 95/12598, WO 95/13069, WO 95/14666, WO 95/16675, WO 95/16692, WO 95/17422, WO 95/17423, WO 95/34311, WO 96/02530 and WO 96/22997. The instant compounds are low molecular weight peptide analogs for promoting the release of growth hormone which have good stability in a variety of physiological environments and which may be administered parenterally, nasally or by the oral route.

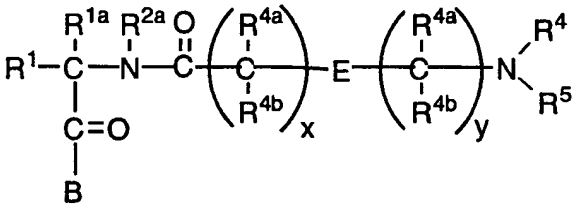
SUMMARY OF THE INVENTION

The instant invention is directed to certain piperidines, pyrrolidines, and hexahydro-1H-azepines which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food or wool production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the piperidine compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe

compositions containing the piperidine compounds for the use of treating humans and animals so as to increase the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

The novel piperidines, pyrrolidines, and hexahydro-1H-azepines of the instant invention are described by structural Formula I:



Formula I

wherein:

R^1 is selected from the group consisting of:

C_1-C_{10} alkyl, -aryl-, aryl (C_1-C_6 alkyl)-,
heteroaryl-, heteroaryl(C_1-C_6 alkyl)-,
(C_3-C_7 cycloalkyl)-(C_1-C_6 alkyl)-,
(C_1-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
aryl-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
heteroaryl-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, and
(C_3-C_7 cycloalkyl)-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
wherein K is -O-, -$S(O)_m$-, -$N(R^2)C(O)$-, -$C(O)N(R^2)$-,-OC(O)-,
-C(O)O-, -CR^2=CR^2- or -C≡C-,
wherein R^2 and the alkyl groups may be further substituted with 1 to 9 halo, -$S(O)_mR^{2a}$, 1 to 3 of -OR^{2a}, or -$C(O)OR^{2a}$, and wherein aryl is phenyl or naphthyl, and heteroaryl is selected from indolyl, thiophenyl, benzofuranyl, benzothiopheneyl, aza-indolyl, pyridinyl, quinolinyl, and benzimidazolyl, wherein aryl and heteroaryl are unsubstituted or substituted with phenyl, phenoxy, halophenyl, 1 to 3 of -C_1-C_6 alkyl, 1 to 3 of halo, 1 to 2 of -OR^2, methylenedioxy, -$S(O)_mR^2$, 1 to 2 of -CF_3, -

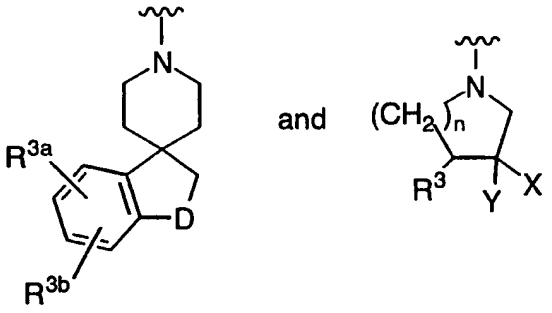
OCF_3, nitro, $-N(R^2)(R^2)$, $-N(R^2)C(O)(R^2)$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, $-N(R^2)SO_2$-aryl, or $-N(R^2)SO_2R^2$;

R^{1a} is hydrogen or C_1-C_4 alkyl;

R^2 is selected from the group consisting of:
hydrogen, $-C_1$-C_6 alkyl, $-C_3$-C_7 cycloalkyl, and $-CH_2$-phenyl,
wherein the alkyl or the cyloalkyl is unsubstituted or substituted with hydroxyl, C_1-C_3 alkoxy, thioalkyl, $C(O)OR^{2a}$, and where, if two $-C_1$-C_6 alkyl groups are present on one atom, they may be joined to form a C_3-C_8 cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, optionally substituted by hydroxyl;

R^{2a} is hydrogen or C_1-C_6 alkyl;

B is selected from:

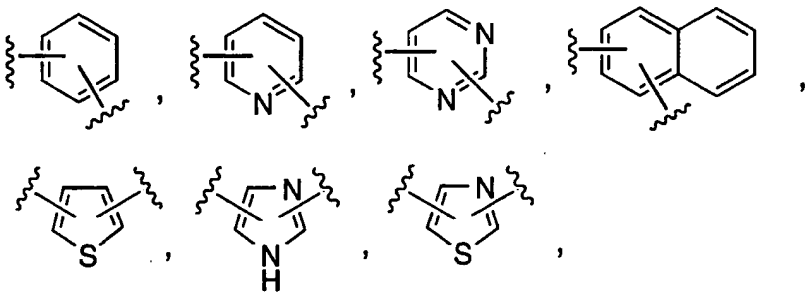


R^3 is selected from: hydrogen, $-(CH_2)_r$phenyl, $-(CH_2)_r$pyridyl, $-(CH_2)_r$thienyl, $-(CH_2)_r$benzimidazolyl, $-(CH_2)_r$quinolinyl, $-(CH_2)_r$naphthyl, $-(CH_2)_r$indolyl, $-C_1$-C_{10} alkyl, $-C_3$-C_7 cycloalkyl, where the phenyl, pyridyl, naphthyl, indolyl, thienyl, benzimidazolyl, quinolinyl, and C_3-C_7 cycloalkyl rings may be substituted by 1 to 3 substituents selected from the group consisting of: C_1-C_6 alkyl, halogen, $-OR^2$, $-NHSO_2CF_3$, $-(CH_2)_rOR^6$, $-(CH_2)_rN(R^2)(R^6)$, $-(CH_2)_r(R^6)$, $-(CH_2)_rC(O)OR^2$, $-(CH_2)_rC(O)OR^6$, $-(CH_2)_rOC(O)R^2$, -

$(CH_2)_rOC(O)R^6$, $-(CH_2)_rC(O)R^2$, $-(CH_2)_rC(O)R^6$, $-(CH_2)_rC(O)N(R^2)(R^2)$, $-(CH_2)_rC(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)C(O)(R^2)$, $-(CH_2)_rN(R^2)C(O)R^6$ $-(CH^2)_rN(R^6)C(O)R^2$, $-(CH_2)_rN(R^6)C(O)R^6$, $-(CH_2)_rN(R^2)C(O)OR^2$, $-(CH_2)_rN(R^2)C(O)OR^6$, $-(CH_2)_rN(R^6)C(O)OR^2$, $-(CH_2)_rN(R^6)C(O)OR^6$, $-(CH_2)_rN(R^2)C(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)C(O)N(R^2)(R^2)$, $-(CH_2)_rN(R^6)C(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)SO_2R^2$, $-(CH_2)rN(R^6)SO_2R^2$, $-(CH_2)_rN(R^6)SO_2R^6$, $-(CH_2)_rOC(O)N(R^2)(R^6)$, $-(CH_2)_rOC(O)N(R^2)(R^2)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rOC(O)N(R^2)(R^2)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^2)$, $-(CH_2)_rN(R^2)SO_2N(R^2)(R^6)$, $-(CH_2)_rN(R^6)SO_2N(R^2)(R^6)$, $-(CH_2)_rS(O)_mR^6$, and $-(CH_2)_rS(O)_mR^2$;

R^{3a} and R^{3b} are independently selected from: hydrogen, phenyl, phenoxy, halophenyl, $-C_1$-C_6 alkyl, halogen, $-OR^2$, methylenedioxy, $-S(O)_mR^2$, $-CF_3$, $-OCF_3$, nitro, $-N(R^2)(R^2)$, $-N(R^2)C(O)(R^2)$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, $-N(R^2)SO_2$-aryl, and $-N(R^2)SO^2R^2$;

E is selected from: -O-, -S-, -CH=CH-,



which is optionally substituted with a substituent selected from: halo, hydroxy, $-N(R^2)(R^2)$, C_1-C_6 alkyl and C_1-C_6 alkoxy;

R^4 and R^5 are independently selected from hydrogen, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl where the substituents are selected from halo, hydroxy, phenyl, and C_1-C_6 alkoxycarbonyl;
or R^5 and R^4 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is $-C(R^2)_2-$, -O-, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3 and R^2 is as defined above;

R^{4a} and R^{4b} are independently selected from: hydrogen, C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^2$, $-S(O)_mR^2$, $-C(O)OR^2$, C_3-C_7 cycloalkyl, $-N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$; or R^{4a} and R^{4b} may independently be joined to one or both of R^4 or E (where E is other than -O-, -S-, or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^{4a} or R^{4b} and the R^4 E group, wherein the bridge contain 1 to 8 carbons atoms; or R^{4a} and R^{4b} may be joined to one another to form C_3-C_7 cycloalkyl;

R^6 is selected from: hydrogen, C_1-C_6 alkyl, and $(CH_2)_v$aryl, wherein the $(CH_2)_v$ and alkyl groups may be optionally substituted by $-O(R^2)$, $-S(O)_mR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, or $-N(R^2)C(O)N(R^2)(R^2)$, wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C_1-C_6 alkyl, C_3-C_6 cycloalkyl, amino, or hydroxyl;

X is selected from the group consisting of: hydrogen, -C≡N, $-(CH_2)_qN(R^2)C(O)R^2$, $-(CH_2)_qN(R^2)C(O)(CH_2)_t$aryl, $-(CH_2)_qN(R^2)SO_2(CH_2)_t$aryl, $-(CH_2)_qN(R^2)SO_2R^2$, $-(CH_2)_qN(R^2)C(O)N(R^2)(CH_2)_t$aryl, $-(CH_2)_qN(R^2)C(O)N(R^2)(R^2)$, $-(CH_2)qC(O)N(R^2)(R^2)$, $-(CH_2)_qC(O)N(R^2)(CH_2)_t$aryl, $-(CH_2)_qC(O)OR^2$, $-(CH_2)_qC(O)O(CH_2)_t$aryl, $-(CH_2)_qOR^2$, $-(CH2)qOC(O)R^2$, $-(CH_2)_qOC(O)(CH^2)_t$aryl, $-(CH_2)_qOC(O)N(R^2)(R^2)$,

$-(CH_2)_qC(O)R^2$, $-(CH_2)_qC(O)(CH_2)_t$aryl, $-(CH_2)_qN(R^2)C(O)OR^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)(R^2)$, $-(CH_2)_qS(O)_mR^2$, and $-(CH_2)_qS(O)_m(CH_2)_t$aryl, where R^2, $(CH_2)_q$ and $(CH_2)_t$ group may be optionally substituted with C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $N(R^2)(R^2)$, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted with halogen, $-OR^2$, $-CON(R^2)(R^2)$, $-C(O)OR^2$, C_1-C_4 alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of:
hydrogen, C_1-C_{10} alkyl, $-(CH_2)_t$aryl, $-(CH_2)_q(C_3$-C_7 cycloalkyl), $-(CH_2)_q$-K-(C_1-C_6 alkyl), $-(CH_2)_q$-K-$(CH_2)_t$aryl, $-(CH_2)_q$-K-$(CH_2)_t(C_3$-C_7 cycloalkyl containing O, NR^2 S) and $-(CH_2)_q$-K-$(CH_2)_t(C_3$-C_7 cycloalkyl), where K is -O-, $-S(O)_m$-, $-C(O)NR^2$-, -CH=CH-, -C≡C-, $-N(R^2)C(O)$-, $-C(O)NR^2$-, -C(O)O-, or -OC(O)-, and where the alkyl, R^2, $(CH_2)q$ and $(CH_2)_t$ groups are optionally substituted by C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $-CONH_2$ or a carboxylate C_1-C_4 alkyl ester, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazoly, indolyl, oxadiazoyl, pyrimidinyl, thiadiazolyl,pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrrazinyl, or isothiazolyl which is optionally substituted with halogen, $-OR^2$, $-C(O)OR^2$, $N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, C_1-C_4 alkyl, $-S(O)_mR^2$, or 1H-tetrazol-5-yl;

D is selected from: $-N(R^7)$-, $-S(O)_m$-, -C(O)- and $-C(H)(R^7)$-, wherein R^7 is selected from: $-R^2$, $-OR^2$, $-(CH_2)_q$aryl, $-C(O)R^2$, $-C(O)(CH_2)_q$aryl, $-SO_2R^2$, $-SO_2(CH_2)_q$aryl, $-C(O)N(R^2)(R^2)$, $-C(O)N(R^2)(CH_2)_q$aryl, $-C(O)OR^2$, 1-H-tetrazol-5-yl, $-SO_2N(R^2)$aryl, $-SO_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C_1-C_4 alkyl, and the R^2 and aryl may be optionally further substituted with a substituent selected from: $-OR^{2a}$, $-O(CH_2)_q$ aryl, $-C(O)OR^{2a}$, -

$C(O)(CH_2)_q$ aryl, $-C(O)N(R^{2a})(R^{2a})$, $-C(O)N(R^{2a})(CH_2)_1$ aryl, halogen, $-N(R^{2a})(R^{2a})$, $-C_1$-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $-C(O)NHSO_2R^{2a}$, $-S(O)_mR^{2a}$, $-C(O)NHSO_2(CH_2)_q$aryl, $-N(R^2)C(O)N(R^{2a})(R^{2a})$, $-N(R^{2a})C(O)N(R^{2a})(CH_2)_q$aryl, $-N(R^{2a})(R^{2a})$, $-N(R^{2a})C(O)R^{2a}$, $-N(R^{2a})C(O)(CH_2)_q$ aryl, $-OC(O)N(R^{2a})(R^{2a})$, $-OC(O)N(R^{2a})(CH_2)_q$ aryl;

1 is 0, 1 or 2;
m is 0, 1, or 2;
n is 0, 1, or 2;
q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2;
x is 0, 1, 2, or 3;
y is 0, 1, 2, or 3, with the proviso that if E is -O- or -S-, y is other than 0 or 1, and with the further proviso that if E is -CH=CH-, y is other than 0;

and pharmaceutically acceptable salts and individual diastereomers thereof.

In the above structural formula and throughout the instant specification, the following terms have the indicated meanings:

When n is 1 a pyrrolidine ring is formed, when n is 2 a piperidine ring is formed, and when n is 3 the ring is designated a hexahydro-1-H-azepine.

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration and if two carbon atoms or more they may include a double or a triple bond. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propargyl, and the like .

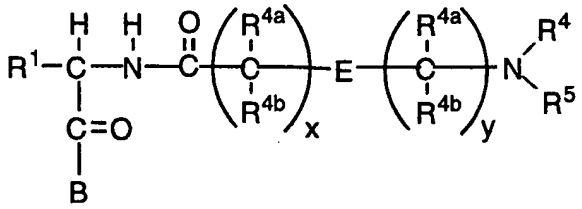
The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" within the present invention, unless otherwise specified, is intended to include aromatic rings, such as carbocyclic and heterocyclic aromatic rings selected the group consisting of: phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrrazinyl, or isothiazolyl, which may be optionally substituted by 1 to 3 of C_1-C_6 alkyl, 1 to 3 of halogen, 1 to 2 of OR_2, methylenedioxy, $-S(O)_mR_2$, 1 to 2 of $-CF_3$, $-OCF_3$, nitro, $-N(R_2)C(O)(R_2)$, $-C(O)OR_2$, $-C(O)N(R_2)(R_2)$, -1H-tetrazol-5-yl, $-SO_2N(R_2)(R_2)$, $-N(R_2)SO_2$ phenyl, or $-N(R_2)SO_2R_2$, wherein R_2 is as defined herein.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Preferred compounds of the instant invention include those of Formula Ia:



Formula Ia

wherein:

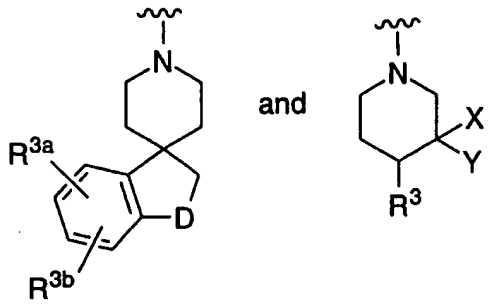
R^1 is selected from the group consisting of:

C_1-C_{10} alkyl, -aryl-, aryl (C_1-C_6 alkyl)-, heteroaryl-, heteroaryl(C_1-C_6 alkyl)-,

(C_3-C_7 cycloalkyl)-(C_1-C_6 alkyl)-,
(C_1-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
aryl-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
heteroaryl-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, and
(C_3-C_7 cycloalkyl)-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
wherein K is -O-, -$S(O)_m$-, -$N(R^2)C(O)$-, -$C(O)N(R^2)$-,-OC(O)-, -C(O)O-, -CR^2=CR^2- or -C≡C-,
wherein R^2 and the alkyl groups may be further substituted with 1 to 9 halo, -$S(O)_mR^{2a}$, 1 to 3 of -OR^{2a}, or -$C(O)OR^{2a}$, and wherein aryl is phenyl or naphthyl, and heteroaryl is selected from indolyl, thiophenyl, benzofuranyl, benzothiopheneyl, aza-indolyl, pyrindinyl, quinolinyl, and benzimidazolyl, wherein aryl and heteroaryl are unsubstituted or substituted with phenyl, phenoxy, halophenyl, 1 to 3 of -C_1-C_6 alkyl, 1 to 3 of halo, 1 to 2 of -OR^2, methylenedioxy, -$S(O)_mR^2$, 1 to 2 of -CF_3, -OCF_3, nitro, -$N(R^2)(R^2)$, -$N(R^2)C(O)(R^2)$, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, -$SO_2N(R^2)(R^2)$, -$N(R^2)SO_2$-aryl, or -$N(R^2)SO_2R^2$;

R^2 is selected from the group consisting of:
hydrogen, -C_1-C_6 alkyl, -C_3-C_7 cycloalkyl, and -CH_2-phenyl,
wherein the alkyl or the cyloalkyl is unsubstituted or substituted with hydroxyl, C_1-C_3 alkoxy, thioalkyl, -$C(O)OR^{2a}$, and wherein, if two -C_1-C_6 alkyl groups are present on one atom, the groups may be optionally joined to form a C_3-C_8 cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine;

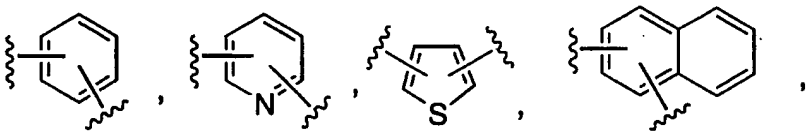
B is selected from:



R^3 is selected from: hydrogen, phenyl, pyridyl, naphthyl, indolyl, benzimidazolyl, thienyl, quinolinyl, where the phenyl, pyridyl, naphthyl, benzimidazolyl, thienyl, quinolinyl, and indolyl may be substituted by 1 to 3 substituents selected from the group consisting of: C_1-C_6 alkyl, halogen, $-OR^2$, $-(CH_2)_rOR^6$, $-(CH_2)_rN(R^2)(R^6)$, $-(CH_2)_r(R^6)$, $-(CH_2)_rC(O)OR^2$, $-(CH_2)_rC(O)OR^6$, $-(CH_2)_rC(O)R^2$, $-(CH_2)_rC(O)R^6$, $-(CH_2)_rC(O)N(R^2)(R^2)$, $-(CH_2)_rC(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)C(O)(R^2)$, $-(CH_2)_rN(R^2)C(O)R^6$ $-(CH_2)_rN(R^6)C(O)R^2$, $-(CH_2)_rN(R^6)C(O)R^6$, $-(CH_2)_rN(R^2)C(O)OR^2$, $-(CH_2)_rN(R^2)C(O)OR^6$, $-(CH_2)_rN(R^6)C(O)OR^2$, $-(CH_2)_rN(R^6)C(O)OR^6$, $-(CH_2)_rN(R^2)C(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)C(O)N(R^2)(R^2)$, $-(CH_2)_rN(R^6)C(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)SO_2R^2$, $-(CH_2)_rN(R^6)SO_2R^2$, $-(CH_2)_rN(R^6)SO_2R^6$, $-(CH_2)_rOC(O)N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^2)$, $-(CH_2)_rS(O)_mR^6$, and $-(CH_2)_rS(O)_mR^2$;

R^{3a} and R^{3b} are independently selected from: hydrogen, phenyl, phenoxy, halophenyl, $-C_1$-C_6 alkyl, halogen, $-OR^2$, methylenedioxy, $-S(O)_mR^2$, $-CF_3$, $-OCF_3$, nitro, $-N(R^2)(R^2)$, $-N(R^2)C(O)(R^2)$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, $-N(R^2)SO_2$-aryl, and $-N(R^2)SO^2R^2$;

E is selected from: -O-, -S-, -CH=CH-,



which is optionally substituted with a substituent selected from: halo, hydroxy, -N(R^2)(R^2), C_1-C_6 alkyl and C_1-C_6 alkoxy;

R^4 and R^5 are independently selected from hydrogen, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl where the substituents are selected from halo, hydroxy, phenyl, and C_1-C_6 alkoxycarbonyl;
or R^5 and R^4 may be taken together to form -$(CH_2)_d$-$L_a$$(CH_2)_e$- where L_a is -$C(R^2)_2$-, -O-, -$S(O)_m$- or -$N(R^2)$-, d and e are independently 1 to 3 and R^2 is as defined above;

R^{4a} and R^{4b} are independently selected from: hydrogen, C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, -OR^2, -$S(O)_mR^2$, -$C(O)OR^2$, C_3-C_7 cycloalkyl, -N(R^2)(R^2), -C(O)N(R^2)(R^2); or R^{4a} and R^{4b} may independently be joined to one or both of R^4 or E (were E is other than -O-, -S-, or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^{4a} or R^{4b} and the R^4 E group, wherein the bridge contain 1 to 5 carbons atoms; or R^{4a} and R^{4b} may be joined to one another to form C_3-C_7 cycloalkyl;

R^6 is selected from: hydrogen, C_1-C_6 alkyl, and $(CH_2)_v$aryl, wherein the $(CH_2)_v$ and alkyl groups may be optionally substituted by -O(R^2), -$S(O)_mR^2$, -$C(O)OR^2$, -C(O)N(R^2)(R^2), -SO_2N(R^2)(R^2), or -N(R^2)C(O)N(R^2)(R^2), wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C_1-C_6 alkyl, C_3-C_6 cycloalkyl, amino, or hydroxyl;

X is selected from the group consisting of: hydrogen, -C≡N, -$(CH_2)_qN(R^2)C(O)R^2$, -$(CH_2)_qN(R^2)C(O)(CH_2)_t$aryl, -$(CH_2)_qN(R^2)SO_2(CH_2)_t$aryl, -$(CH_2)_qN(R^2)SO_2R^2$, -$(CH_2)_qN(R^2)C(O)N(R^2)(CH_2)_t$aryl, -$(CH_2)_qN(R^2)C(O)N(R^2)(R^2)$, -$(CH_2)_qC(O)N(R^2)(R^2)$, -$(CH_2)_qC(O)N(R^2)(CH_2)_t$aryl, -$(CH_2)_qC(O)OR^2$, -$(CH_2)_qC(O)O(CH_2)_t$aryl, -$(CH_2)_qOR^2$, -$(CH_2)_qOC(O)R^2$, -$(CH_2)_qOC(O)(CH^2)_t$aryl, -$(CH_2)_qOC(O)N(R^2)(R^2)$, -$(CH_2)_qC(O)R^2$, -$(CH_2)_qC(O)(CH_2)_t$aryl, -$(CH_2)_qN(R^2)C(O)OR^2$, -$(CH_2)_qN(R^2)SO_2N(R^2)(R^2)$, -$(CH_2)_qS(O)_mR^2$, and -$(CH_2)_qS(O)_m(CH_2)_t$aryl, where R^2, $(CH_2)_q$ and $(CH_2)_t$ group may be optionally substituted with C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $N(R^2)(R^2)$, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted with halogen, -OR^2, -$CON(R^2)(R^2)$, -$C(O)OR^2$, C_1-C_4 alkyl, -$S(O)_mR^2$, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of:
hydrogen, C_1-C_{10} alkyl, -$(CH_2)_t$aryl, -$(CH_2)_q(C_3$-C_7 cycloalkyl), -$(CH_2)_q$-K-(C_1-C_6 alkyl), -$(CH_2)_q$-K-$(CH_2)_t$aryl, -$(CH_2)_q$-K-$(CH_2)_t(C_3$-C_7 cycloalkyl containing O, NR^2 S) and -$(CH_2)_q$-K-$(CH_2)_t(C_3$-C_7 cycloalkyl), where K is O, $S(O)_m$, $C(O)NR^2$, CH=CH, C≡C, $N(R^2)C(O)$, $C(O)NR^2$, C(O)O, or OC(O), and where the alkyl, R^2, $(CH_2)q$ and $(CH_2)_t$ groups are optionally substituted by C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, -$CONH_2$ or a carboxylate C_1-C_4 alkyl ester, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazoly, indolyl, oxadiazoyl, pyrimidinyl, thiadiazolyl,pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrrazinyl, or isothiazolyl which is optionally substituted with halogen, -OR^2, -$C(O)OR^2$, $N(R^2)(R^2)$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, C_1-C_4 alkyl, -$S(O)_mR^2$, or 1H-tetrazol-5-yl;

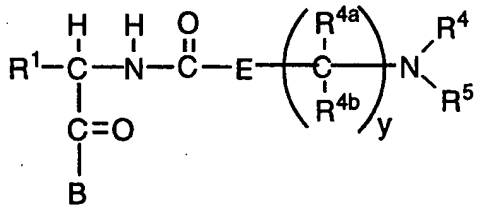
D is selected from: -$N(R^7)$-, -$S(O)_m$-, -C(O)- and -$C(H)(R^7)$-,

wherein R^7 is selected from: $-R^2$, $-(CH_2)_q$aryl, $-C(O)R^2$, $-SO_2R^2$, $-C(O)N(R^2)(R^2)$, $-C(O)OR^2$, 1-H-tetrazol-5-yl, $-SO_2N(R^2)$aryl, $-SO_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C_1-C_4 alkyl, and the R^2 and aryl may be optionally further substituted with a substituent selected from: $-OR^{2a}$, $-C(O)OR^{2a}$, $-C(O)N(R^{2a})(R^{2a})$, halogen, $-C_1$-C_4 alkyl, and the aryl is selected from of triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, and 1H-tetrazolyl;

l is 0, 1 or 2;
m is 0, 1, or 2;
q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2;
x is 0, 1, 2, or 3;
y is 0, 1, 2, or 3, with the proviso that if E is -O- or -S-, y is other than 0 or 1, and with the further proviso that if E is -CH=CH-, y is other than 0;

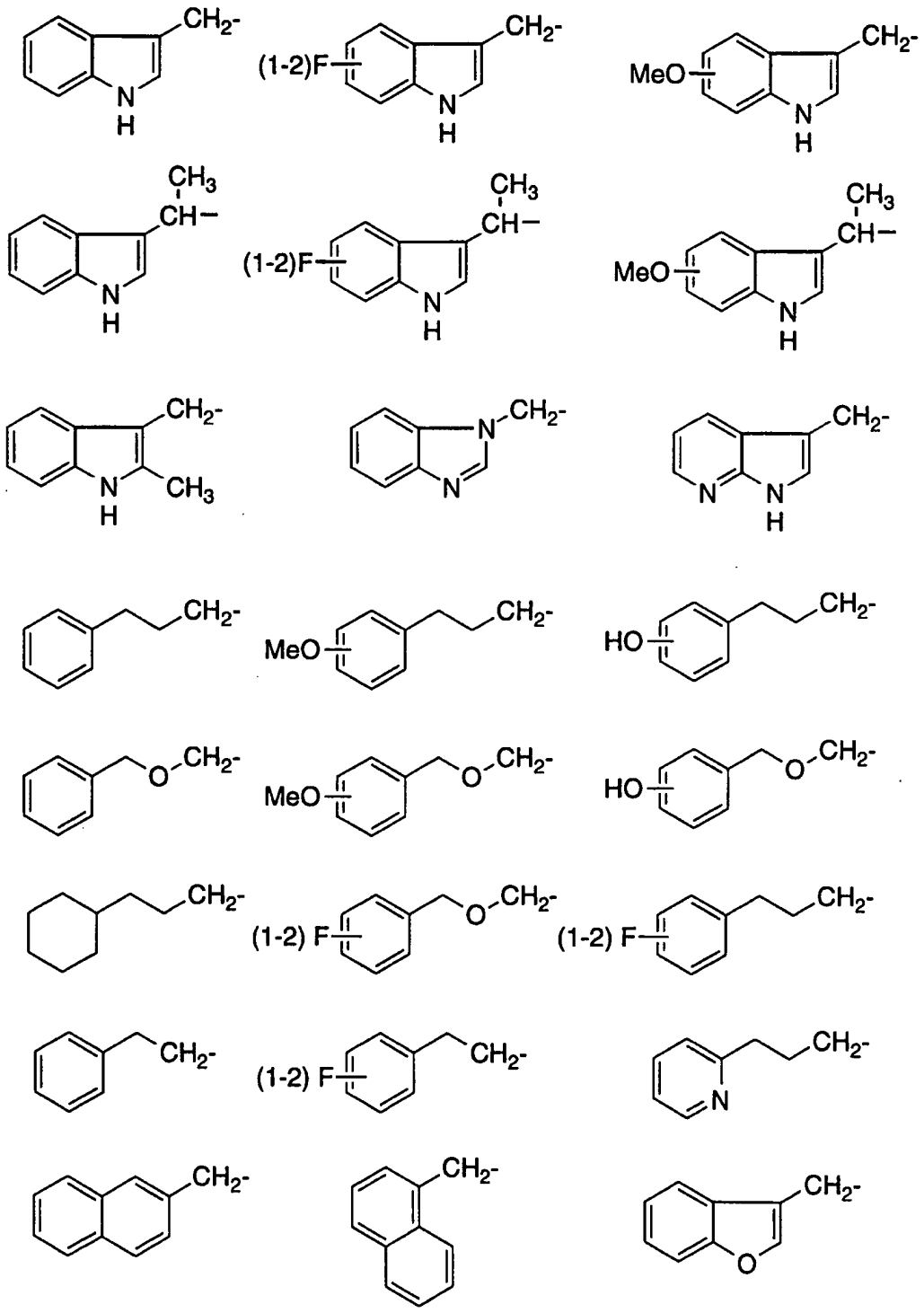
and pharmaceutically acceptable salts and individual diastereomers thereof.

More preferred compounds of the instant invention include those of Formula Ib:



Formula Ib

wherein:
R^1 is selected from the group consisting of:

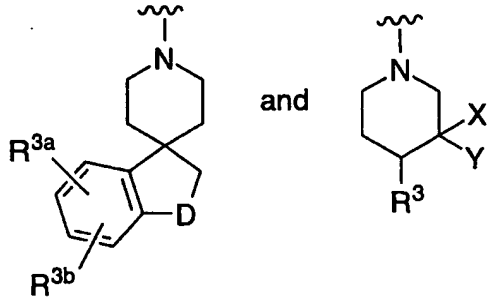

CH2-
N
H
(1-2)F
MeO
CH3
CH
CH3
CH
CH3
CH
N
CH2-
CH3
N
CH2-
N
CH2-
N
H
CH2-
MeO
CH2-
HO
CH2-
O
CH2-
MeO
O
CH2-
HO
O
CH2-
CH2-
(1-2) F
O
CH2-
CH2-
(1-2) F
CH2-
(1-2) F
CH2-
CH2-
N
CH2-
CH2-
O

or their regioisomers where not specified;

R^2 is selected from the group consisting of:
hydrogen, -C_1-C_6 alkyl, -C_3-C_7 cycloalkyl, and -CH_2-phenyl,
wherein the alkyl or the cyloalkyl is unsubstituted or substituted with hydroxyl, C_1-C_3 alkoxy, thioalkyl, -C(O)OR^{2a}, and wherein, if two -C_1-C_6 alkyl groups are present on one atom, the groups may be optionally joined to form a C_3-C_8 cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine;

R^{2a} is hydrogen, or C_1-C_4 alkyl;

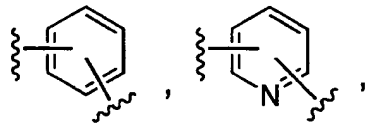
B is selected from:



R^3 is selected from: hydrogen or phenyl, wherein the phenyl is substituted in the ortho position by a substituent selected from the group consisting of: C_1-C_6 alkyl, halogen, $-OR^2$, $-(CH_2)_rOR^6$, $-(CH_2)_rN(R^2)(R^6)$, $-(CH_2)_r(R^6)$, $-(CH_2)_rC(O)OR^2$, $-(CH_2)_rC(O)OR^6$, $-(CH_2)_rC(O)R^2$, $-(CH_2)_rC(O)R^6$, $-(CH_2)_rC(O)N(R^2)(R^2)$, $-(CH_2)_rC(O)N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^2)$, $-(CH_2)_rS(O)_mR^6$, and $-(CH_2)_rS(O)_mR^2$;

R^{3a} and R^{3b} are independently selected from: hydrogen, $-C_1$-C_6 alkyl and halogen;

E is selected from: -O-, -CH=CH-,



which is optionally substituted with a substituent selected from: halo, hydroxy, $-N(R^2)(R^2)$, C_1-C_6 alkyl and C_1-C_6 alkoxy;

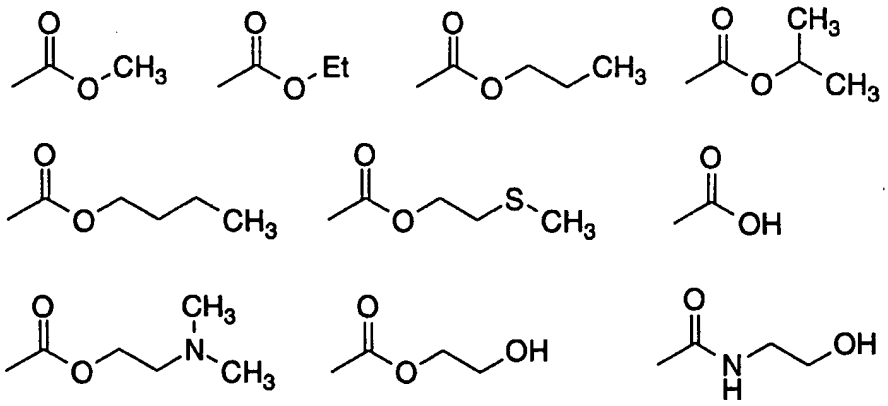
R^4 and R^5 are independently selected from hydrogen, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl where the substituents are selected from halo, hydroxy, phenyl, and C_1-C_6 alkoxycarbonyl;

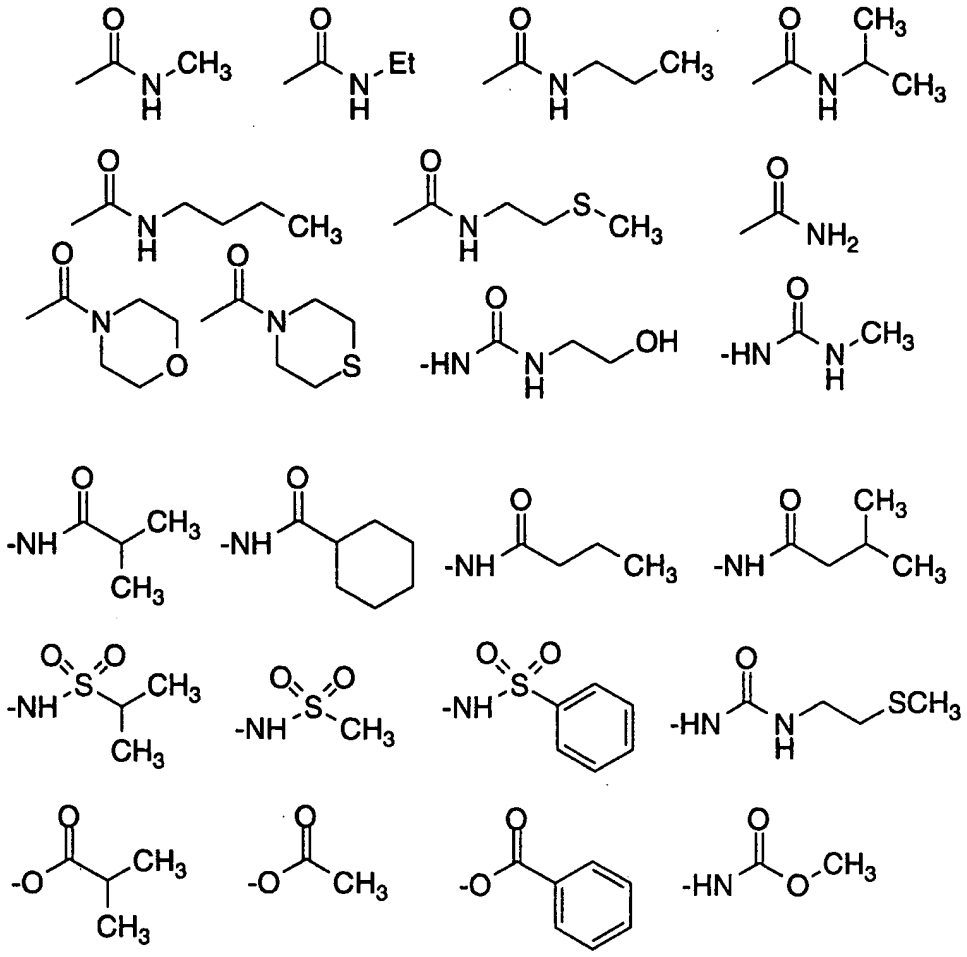
or R^5 and R^4 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is $-C(R^2)_2-$, -O-, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3 and R^2 is as defined above;

R^{4a} and R^{4b} are independently selected from: hydrogen, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, and p-hydroxyphenyl;

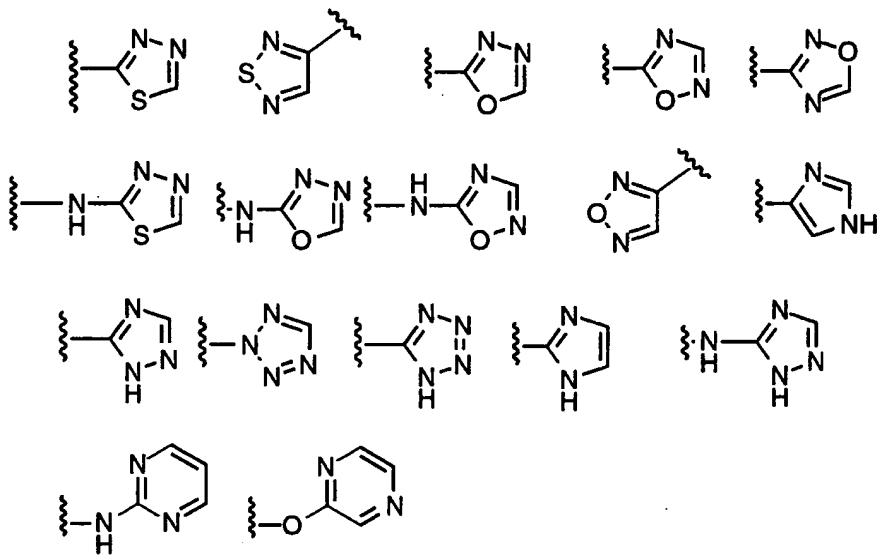
R^6 is selected from: hydrogen, C_1-C_6 alkyl, and $(CH_2)_v$aryl, wherein the $(CH_2)_v$ and alkyl groups may be optionally substituted by $-O(R^2)$, $-S(O)_mR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, or $-N(R^2)C(O)N(R^2)(R^2)$, wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C_1-C_6 alkyl, C_3-C_6 cycloalkyl, amino, or hydroxyl;

X is selected from the group consisting of: hydrogen,



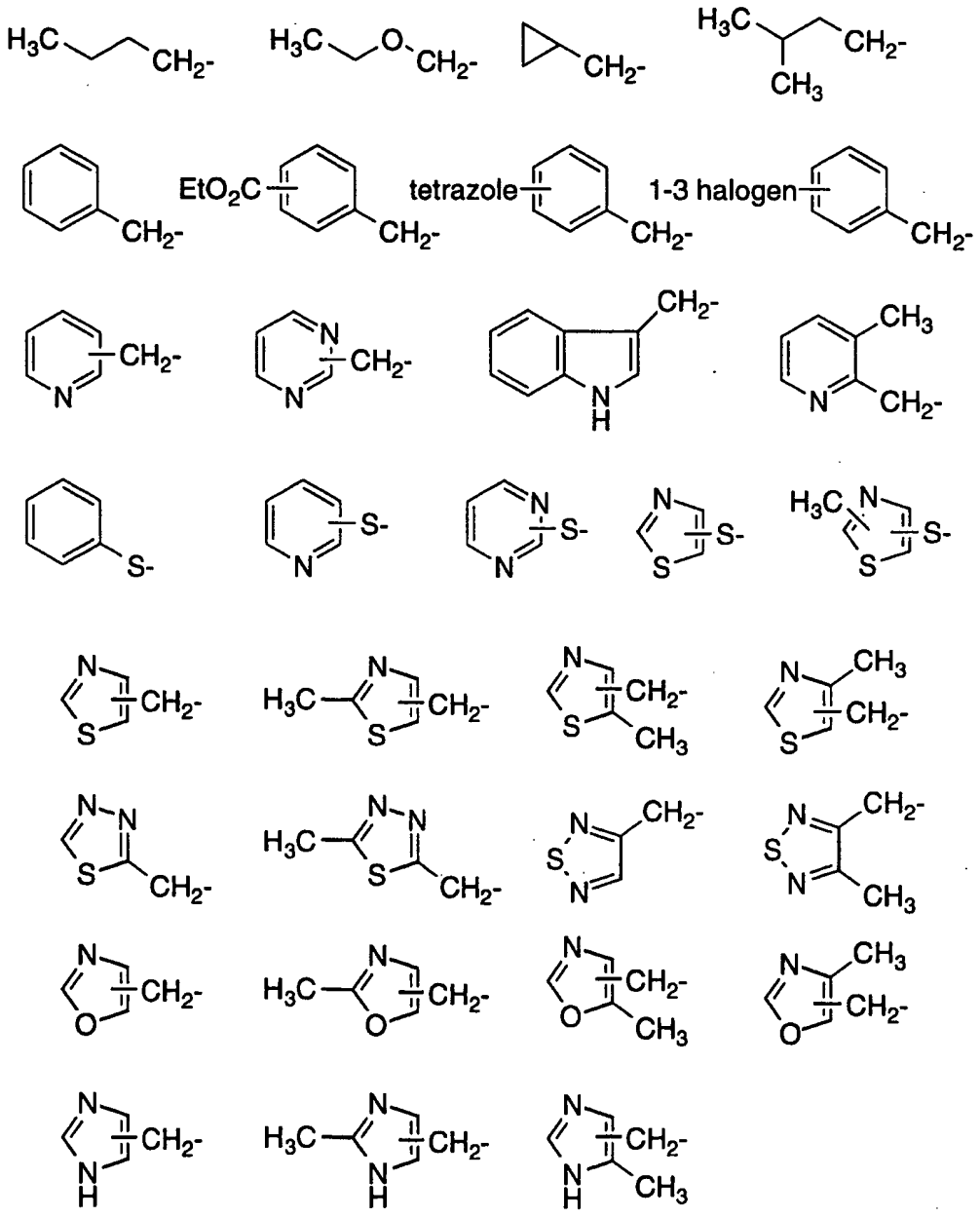


and further selected from the following group of heterocycles



wherein the heterocycle is optionally substituted with a substituent selected from: $-N(R^2)(R^2)$, $-O(R^2)$, C_1-C_3 alkyl, halogen, and trifluoromethyl;

Y is selected from the group consisting of: hydrogen,



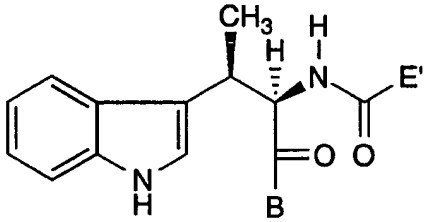
or their regioisomers whereof where not specified;

D is selected from: -N(R^7)-, -S(O)$_m$-, -C(O)- and -C(H)(R^7)-, wherein R^7 is selected from: -R^2, -$(CH_2)_q$aryl, -C(O)R^2, -SO_2R^2, -C(O)N(R^2)(R^2), -C(O)OR^2, 1-H-tetrazol-5-yl, -SO_2N(R^2)aryl, -SO_2N(R^2)(R^2) and the $(CH_2)_q$ may be optionally substituted by C_1-C_4 alkyl, and the R^2 and aryl may be optionally further substituted with a substituent selected from: -OR^{2a}, -C(O)OR^{2a}, -C(O)N(R^{2a})(R^{2a}), halogen, -C_1-C_4 alkyl, and the aryl is selected from of triazolyl, oxadiazolyl, 1H-tetrazolyl, and thiadiazolyl;

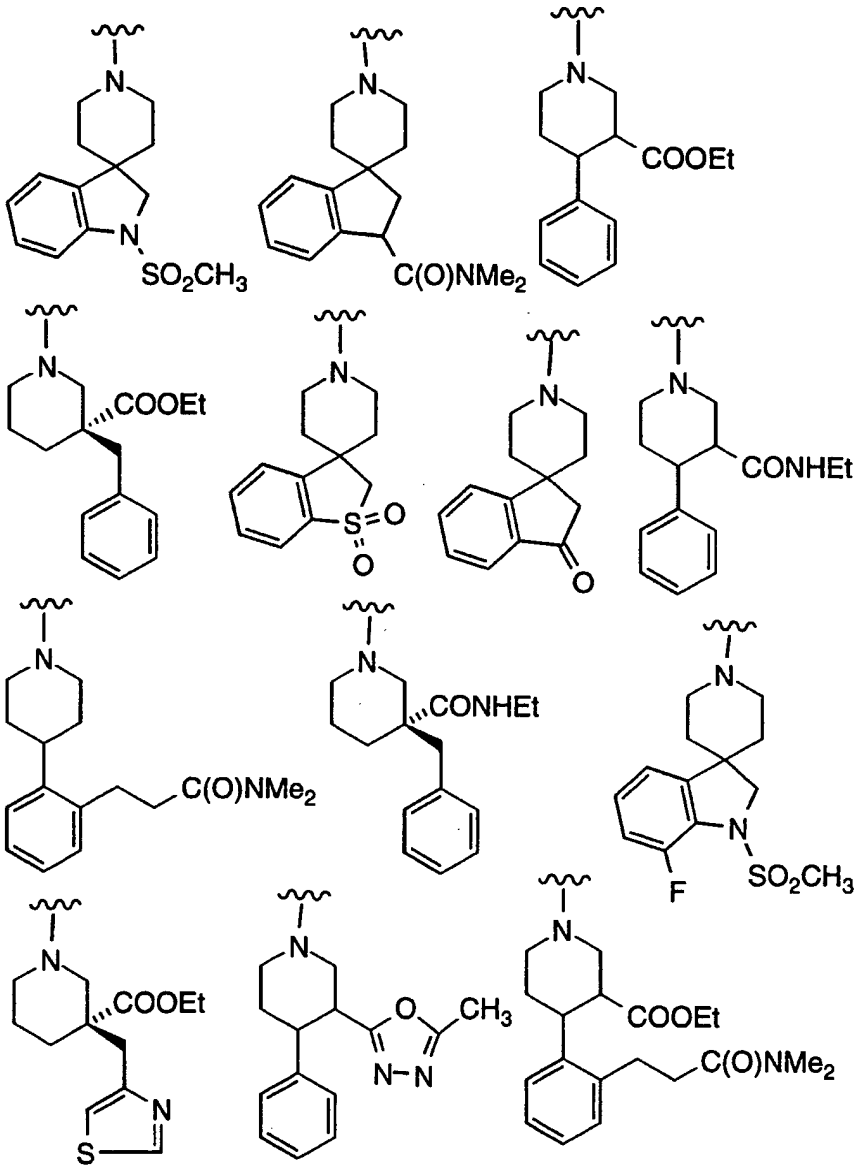
l is 0, 1 or 2;
m is 0, 1, or 2;
q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2;
y is 1 or 2, with the proviso that if E is -O-, y is 2;

and pharmaceutically acceptable salts and individual diastereomers thereof.

The most preferred compounds of the instant invention include compounds of the formula:



wherein B is selected from the group consisting of:



E' is selected from:

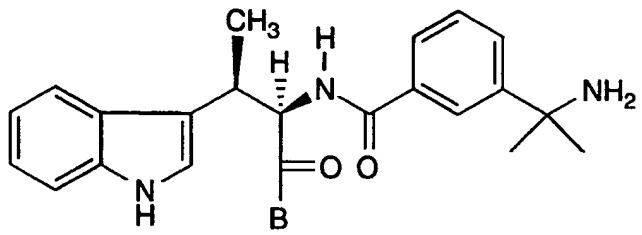
$-CH=CH-CH_2-NH_2$, $-CH=CH-CH(CH_3)-NH_2$,

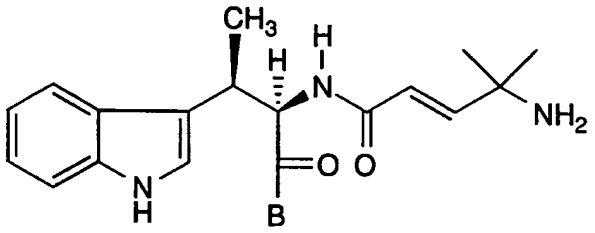
$-CH=CH-C(CH_3)_2-NH_2$,

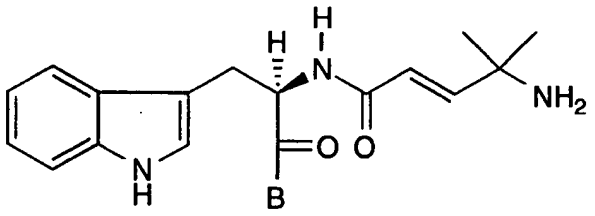
or phenyl substituted with $-CH_2-NH_2$, $-CH(CH_3)-NH_2$, or $-C(CH_3)_2-NH_2$;

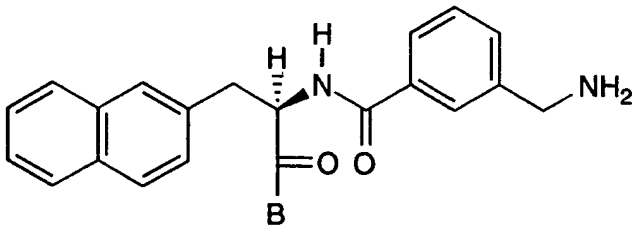
and pharmaceutically acceptable salts and individual diastereomers thereof.

The even more preferred compounds of the instant invention include compounds of the formula:

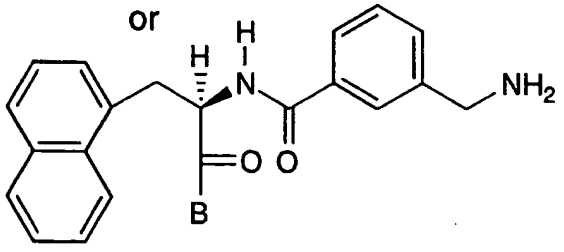




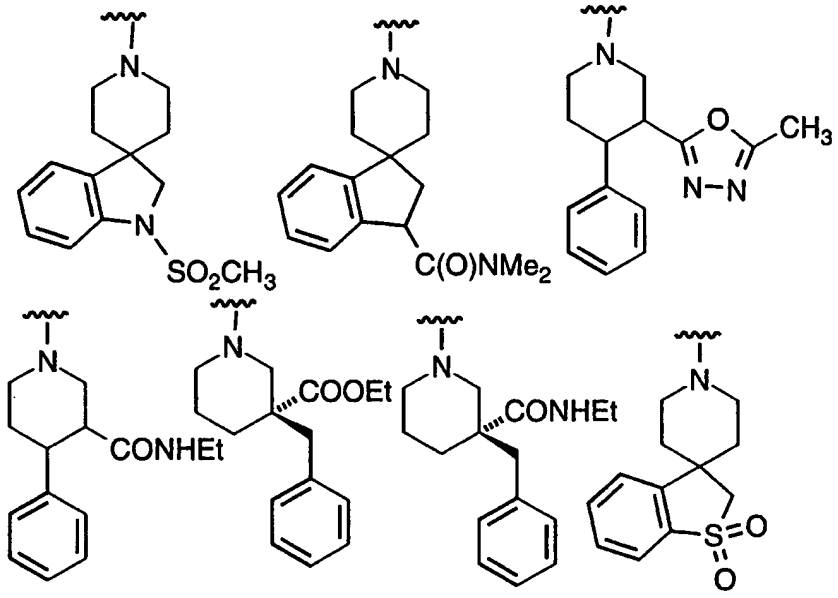




or



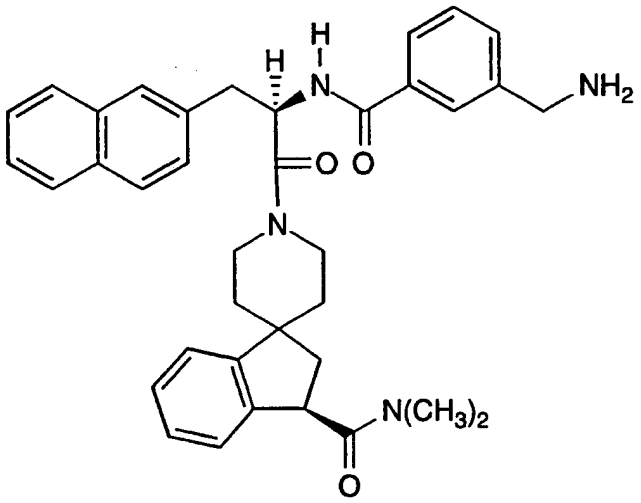
wherein B is selected from the group consisting of:

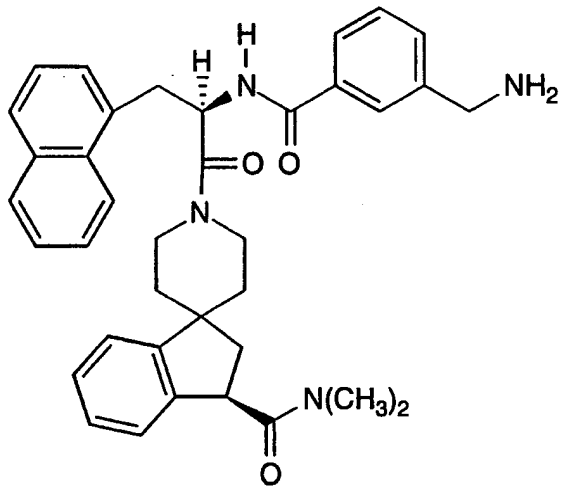


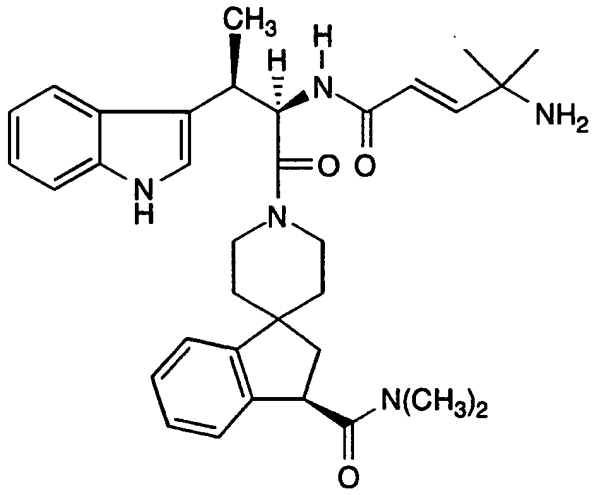
and pharmaceutically acceptable salts and individual diastereomers thereof.

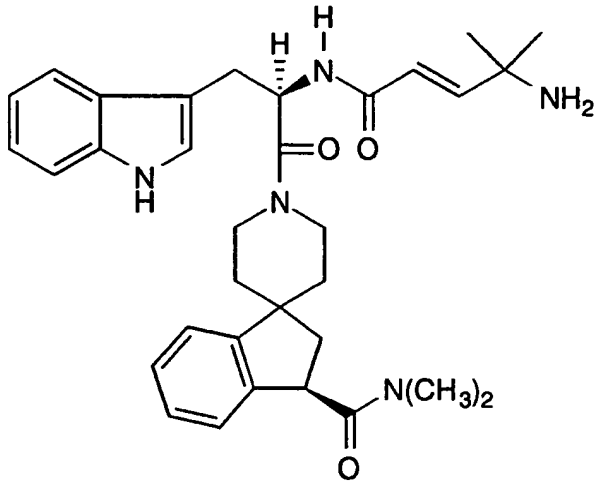
5

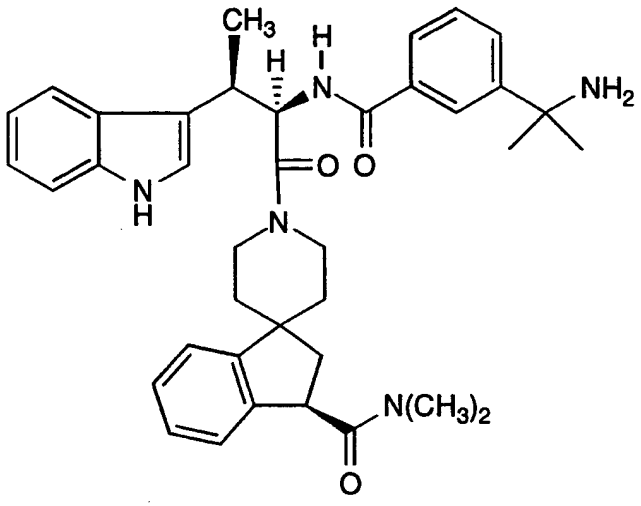
Specific compounds within the instant invention include the following:






CH3
H
H
N
NH2
O
O
N
H
N
N(CH3)2
O


H
H
N
NH2
O
O
N
H
N
N(CH3)2
O



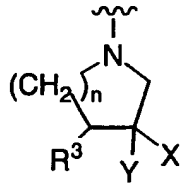
and pharmaceutically acceptable salts and individual diastereomers thereof where not otherwise specified.

Throughout the instant application, the following abbreviations are used with the following meanings:

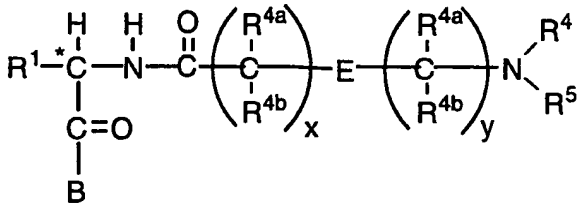
Bu	butyl
Bn	benzyl
BOC, Boc	t-butyloxycarbonyl
BOP	Benzotriazol-1-yloxy tris/dimethylamino)-phosphonium hexafluorophosphate
calc.	calculated
CBZ, Cbz	Benzyloxycarbonyl
DCC	Dicyclohexylcarbodiimide
DMF	N,N-dimethylformamide
DMAP	4-Dimethylaminopyridine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodi-imide hydrochloride
EI-MS	Electron ion-mass spectroscopy
Et	ethyl
eq.	equivalent(s)
FAB-MS	Fast atom bombardment-mass spectroscopy
HOBT, HOBt	Hydroxybenztriazole
HPLC	High pressure liquid chromatography
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LHMDS	Lithium bis(trimethylsilyl)amide
Me	methyl
MF	Molecular formula
MHz	Megahertz
MPLC	Medium pressure liquid chromatography
NMM	N-Methylmorpholine
NMR	Nuclear Magnetic Resonance
Ph	phenyl
Pr	propyl
prep.	prepared
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

TLC	Thin layer chromatography
TMS	Tetramethylsilane

The compounds of the instant invention have at least two asymmetric centers when B is:



and both X and Y are groups other than hydrogen and are different from each other. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixture and as pure or partially purified compounds are included within the ambit of this invention. In the case of the asymmetric center which bears the X and Y groups, in most cases, both R- and S- configurations are consistent with useful levels of growth hormone secretagogue activity. In addition configurations of many of the most preferred compounds of this invention are



Formula I

indicated. When the carbon atom in Formula I bearing an asterisk is of a defined two diastereomers result according to the absolute configuration at the carbon atom bearing the X and Y groups. These diastereomers are arbitrarily referred to as diastereomer 1 (d_1) and diastereomer 2 (d_2) in this invention and, if desired, their independent syntheses or

chromatographic separations may be achieved as described herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counterion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

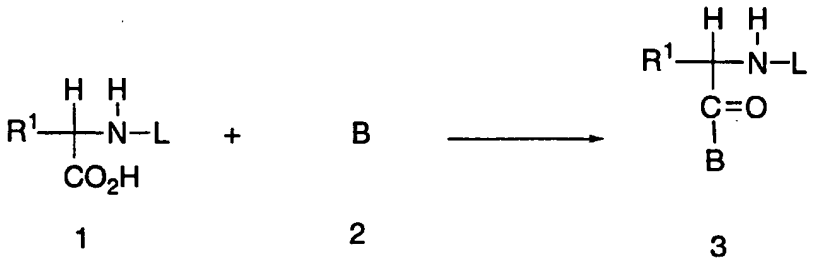
The preparation of compounds of Formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the following reaction schemes.

The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acid to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting groups which may be present and can be found in Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC were used extensively in the synthesis, and their removal conditions are known to those skilled in the art. For example, removal of CBZ groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a nobel metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other

potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid or hydrochloric acid or hydrogen chloride gas.

The protected amino acid derivatives 1 are, in many cases, commercially available, where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives 1 can be prepared by literature methods (Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press: Oxford, 1989). Many of the piperidines, pyrrolidines, and hexahydro-1H-azepines of Formula 2 are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. Some of these methods are illustrated in the subsequent schemes. The skills required in carrying out the reaction and purification of the resulting reaction products are known to those in the art. Purification procedures includes crystallization, normal phase or reverse phase chromatography.

SCHEME 1



1 2 3

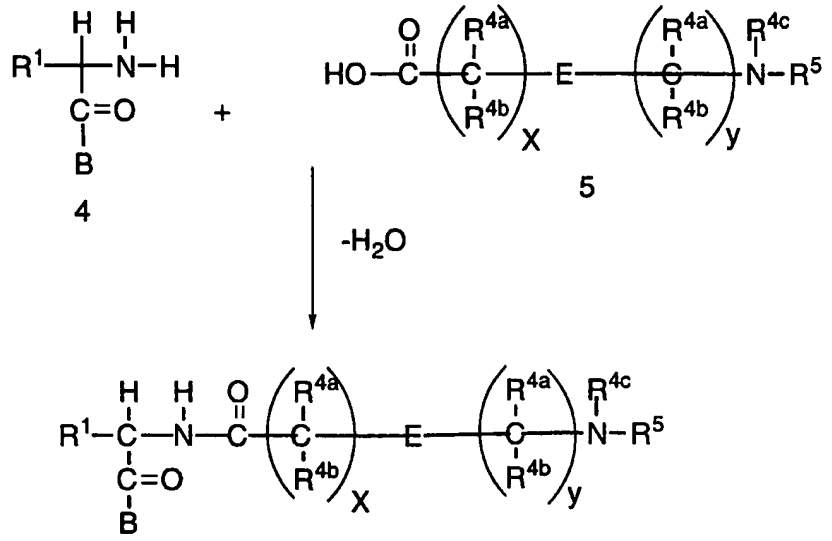
Intermediates of Formula 3 may be synthesized as described in Scheme 1. Coupling of amine of Formula 2, whose preparations are described later if they are not commercially available, to protected amino acids of Formula 1, wherein L is a suitable protecting group, is conveniently carried out under standard peptide coupling conditions.

SCHEME 2

3 4

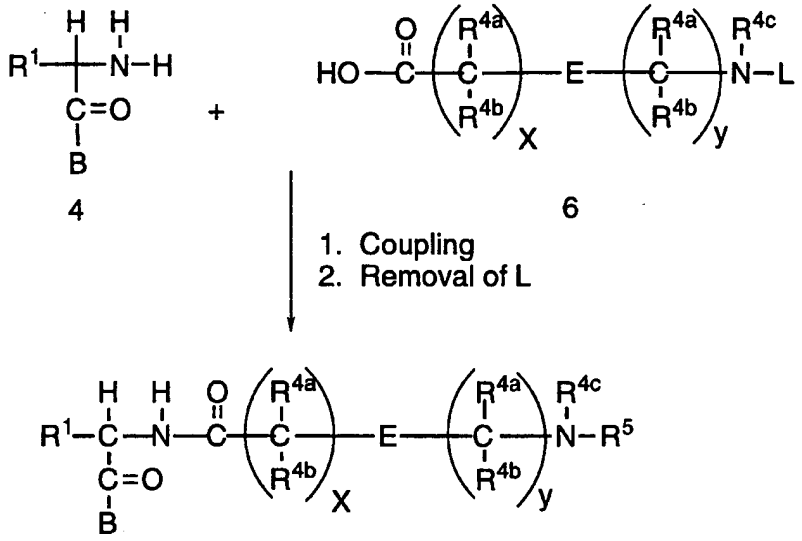
Conversion of 3 to intermediate 4 may be carried out as illustrated in Scheme 2 by removal of the protecting group L (CBZ, BOC, etc.)

SCHEME 3



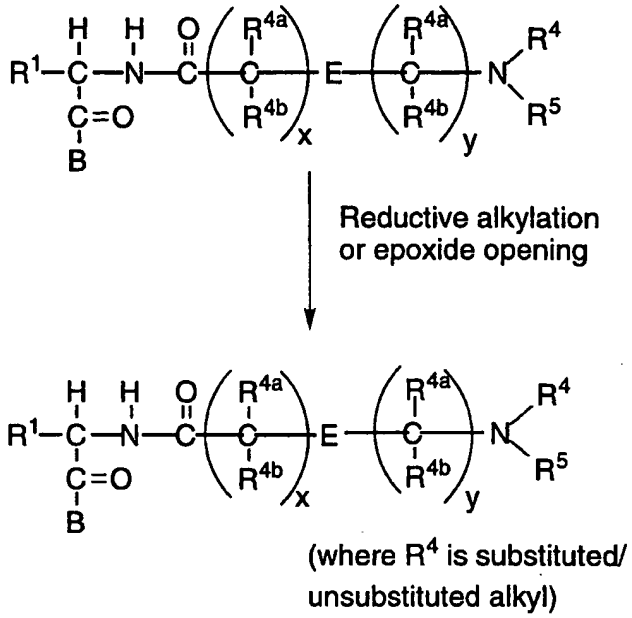
Intermediates of Formula I may be prepared as shown in Scheme 3 by coupling intermediates of Formula 4 to protected amino acids of Formula 5 under the standard peptide-type coupling reaction conditions. The amino acids 5 are either commercially available or can be synthesized by routine methods.

SCHEME 4



As shown in Scheme 4, if R^4 or R^5 is a hydrogen then the protected amino acids 6 are employed in the coupling reaction wherein L is a protecting group as defined above. The removal of L to afford I can be carried out as noted above.

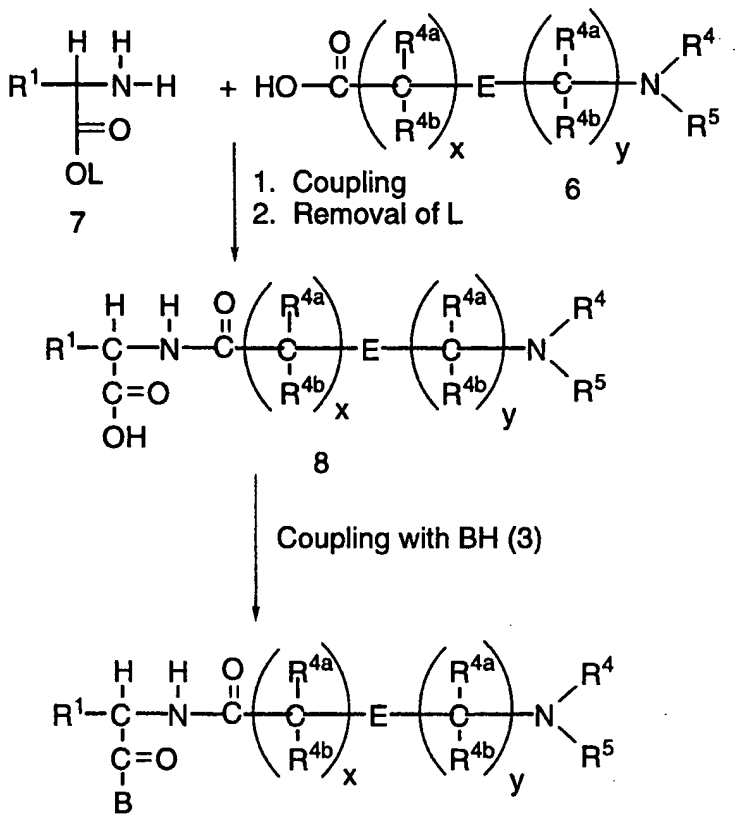
SCHEME 5



Compounds of Formula I wherein R^4 and/or R^5 is a hydrogen may be further elaborated to new Compounds I which are substituted on the amino group as depicted in Scheme 5. Reductive alkylation of I with an aldehyde is carried out under conditions known in the art; for example, by catalytic hydrogenation with hydrogen in the presence of platinum, palladium, or nickel catalysts or with chemical reducing agents such as sodium cyanoborohydride in a protic solvent such as methanol or ethanol in the present of catalytic amount of acid. Alternatively, a similar transformation can be accomplished via an epoxide opening reaction.

The compounds of general Formula I of the present invention may also be prepared in a convergent manner as described in Scheme 6. Intermediates of Formula 7 can be synthesized by well documented methods in the literature. Elaboration of 7 to compounds of Formula 1 can be accomplished as shown in Scheme 6 by coupling intermediates of Formula 7 to amino acids of Formula 6 under standard peptide coupling reaction conditions.

SCHEME 6

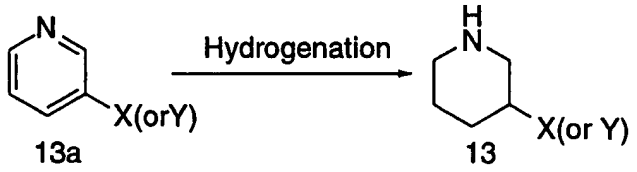


Formula I

Removal of the protecting group L can be accomplished by well documented methods and amines BH of Formula 2 can be coupled to the corresponding acid under standard peptide-type coupling conditions to give compounds of Formula I. When R^4 and/or R^5 is H, substituted alkyl groups may be optionally added to the nitrogen atom as described in Scheme 5.

In the following Schemes preparartions of amines BH of Formula 3 are described.

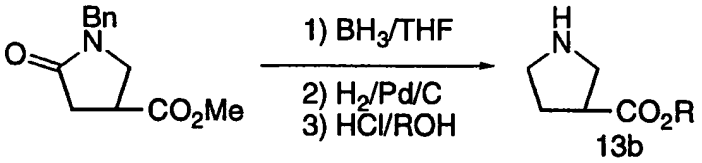
SCHEME 7



13a 13

3-Monosubstituted piperidines of formula 13 can be prepared by the reduction of pyridine derivatives or their salts by hydrogenation in a suitable organic solvent such as water, acetic acid, alcohol, e.g. ethanol, or their mixture, in the presence of a noble metal catalyst such as platinum or an oxide thereof on a support such as activated carbon, and conveniently at room temperature and atmospheric pressure or under elevated temperature and pressure. 3-Monosubstituted piperidines can also be prepared by modification of the X or Y moiety of the existing 3-monosubstituted piperidines.

SCHEME 8



13b

3-Monosubstituted pyrrolidines are commercially available or can be conveniently prepared by literature procedures. Shown in Scheme 8 is an example of the preparation of these compounds via pyrrolidine-3-carboxylic acid ester. The commercially available compound methyl 1-benzyl-4-oxo-3-pyrrolidinecarboxylate is reduced by borane (J. Chem. Soc., 24, 1618-1619). Removal of the benzyl group by catalytic hydrogenolysis followed by ester exchange in an appropriate alcohol medium such as ethyl alcohol in the presence of acid gave the compound 13b. The ester functionality may be further modified through

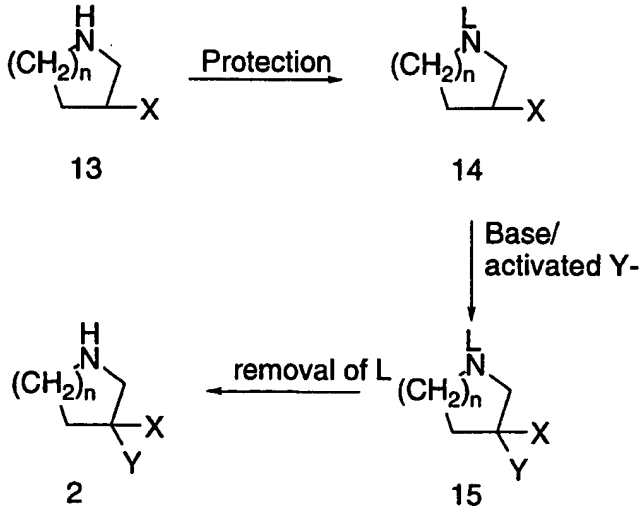
conventional chemistry to other groups as defined by X. 3-Monosubstituted pyrrolidines may also be prepared by catalytic hydrogenation of 3-substituted pyrroles.

SCHEME 9

13c

Hexahydro-1H-azepines are commercially available or may be prepared by the literature procedure. Hexahydro-1H-azepine-3-carboxylic acid (Krogsgaard-Larsen, P. et al., Acta. Chem. Scand., B32, 327, (1978)) is esterified in an alcohol solvent in the presence of acid. The ester functionality may be further modified through conventional chemistry to other groups within the definition of X.

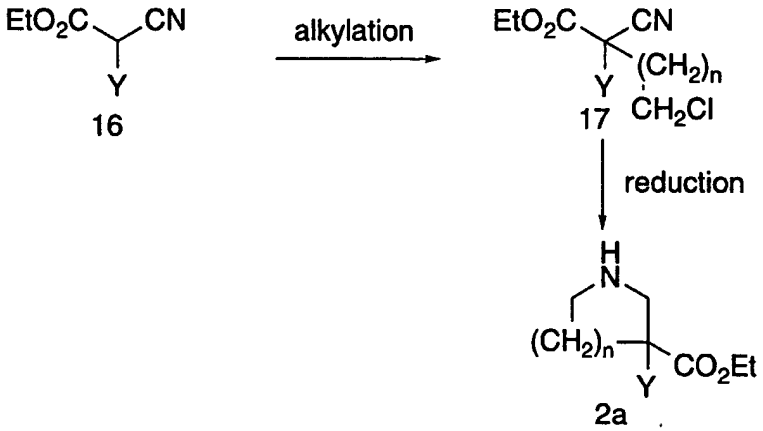
SCHEME 10



Illustrated in Scheme 10 is a general way to prepare di-substituted piperidines, pyrrolidines, and hexahydro-1H-azepines. Compounds of Formula 13 wherein X is an electron withdrawing group

such as -CN, -CO_2R_8, where R_8 is alkyl, aryl, and (C_1-C_4alkyl)aryl are known compounds or may be prepared by methods analogous to those used for the preparation of such known compounds. The secondary amine of compounds of Formula 13 may be first protected by a protecting group L such as BOC and CBZ using the conventional techniques. Introduction of the Y substitution can be achieved by first reacting compounds of Formula 14 with a strong base such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide following by addition of alkylating or acylating reagents such as alkyl halides, aryl alkyl halides, acyl halides, and haloformates in a inert solvent such as THF at temperatures from -100° to room temperature. Thio derivatives where the sulfur is attached directly to an alkyl or an aryl group can be prepared similarly by reacting with a disulfide. The halides used in these reactions are either commercially available or known compounds in the literature or may be prepared by methods analogous to those used for the preparation of known compounds. The protecting group L in compounds of formula 15 may be removed with conventional chemistry to give compounds of Formula 2.

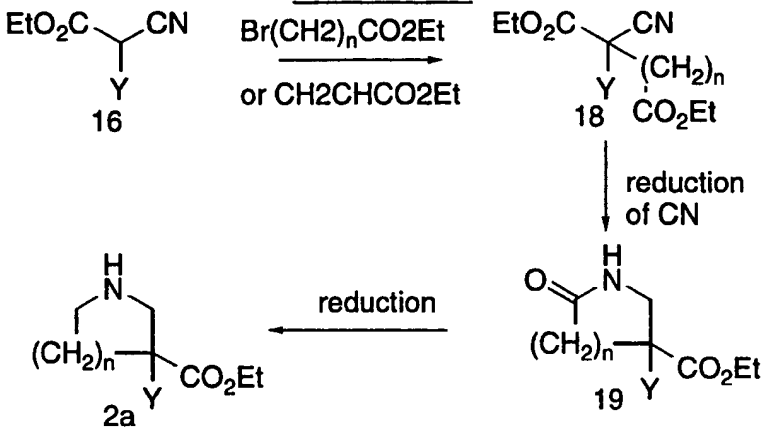
SCHEME 11



Alternative ways of preparing compounds of Formula 2 include construction of the ring itself (Jacoby, R. L. et al, J. Med. Chem., 17, 453-455, (1974)). Alkylation of the cyanoacetates of general formula 16, which are commercially available or may be prepared from literature

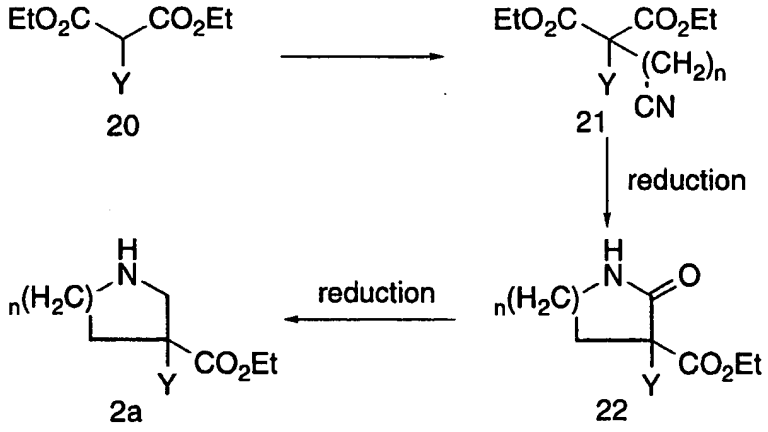
procedures, with alkyl dihalides such as 1-bromo-2-chloroethane or 1-bromo-3-chloropropane yields the chloride 17. Reduction of the nitriles 17 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol to give compounds of Formula 2a.

SCHEME 12



Alternatively, the cyanoacetates of general formula 16 may be alkylated with an ethoxycarbonylalkyl bromide or reacted with ethyl acrylate to give compounds of Formula 18. Reduction of the nitriles 18 by borane or by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam 19. Reduction of the lactam 19 by borane gives compounds of Formula 2a.

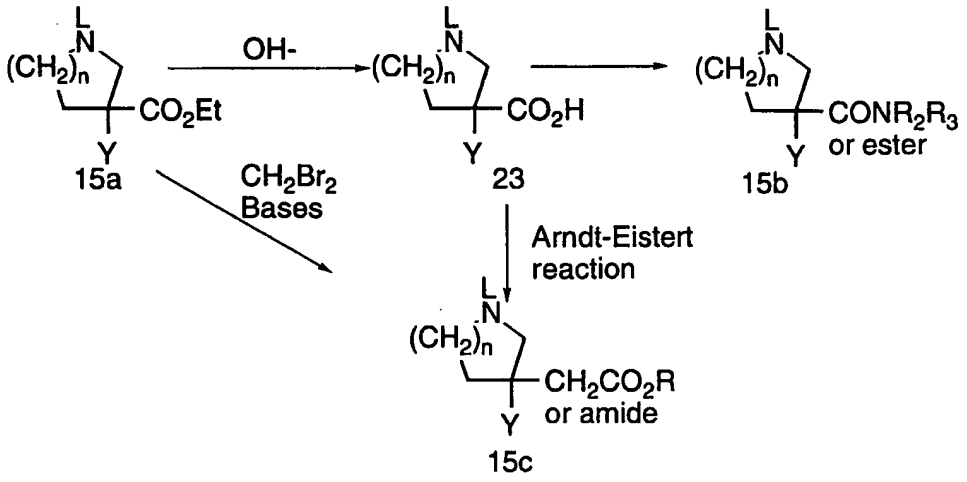
SCHEME 13



Alternatively, a malonate of general formula 20 may be alkylated with cyanoalkyl bromide or can be reacted with acrylonitrile to form compounds of formula 21. Reduction of the nitriles 21 by borane or

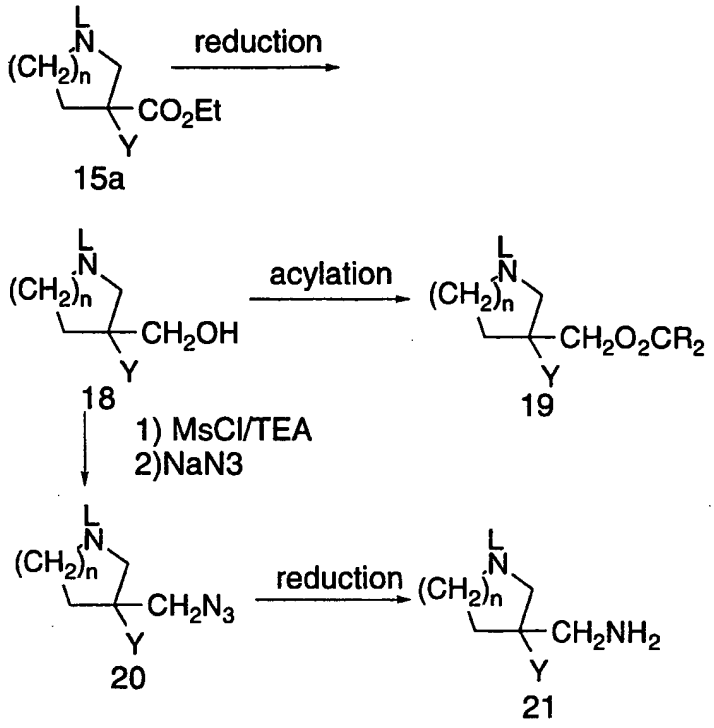
by hydrogenation using Raney Ni as a catalyst gives the corresponding primary amines, which upon refluxing in ethanol gives lactam 22. Reduction of the lactam 22 by borane gives compounds of formula 2a.

SCHEME 14



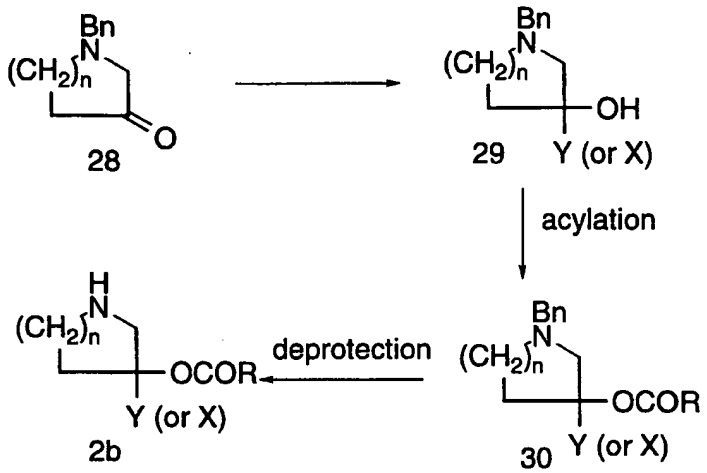
The X, Y functionalities in compounds of general structure 15 may be further elaborated to groups not accessible by direct alkylation. For example in Compound 15 when X = CO_2Et the ester (provided that this is the only ester group in the molecule) can be saponified to the carboxylic acid, which can be further derivatized to amides or other esters. The carboxylic acid can be converted into its next higher homologue, or to a derivative of the homologous acid, such as amide or ester by an Arndt-Eistert reaction. Alternatively, the ester can be directly homologated by the protocol using ynolate anions described by C. J. Kowalski and R. E. Reddy in J. Org. Chem., 57, 7194-7208 (1992). The resulting acid and/or ester may be converted to the next higher homologue, and so on and so forth. The protecting group L may be removed through conventional chemistry.

SCHEME 15



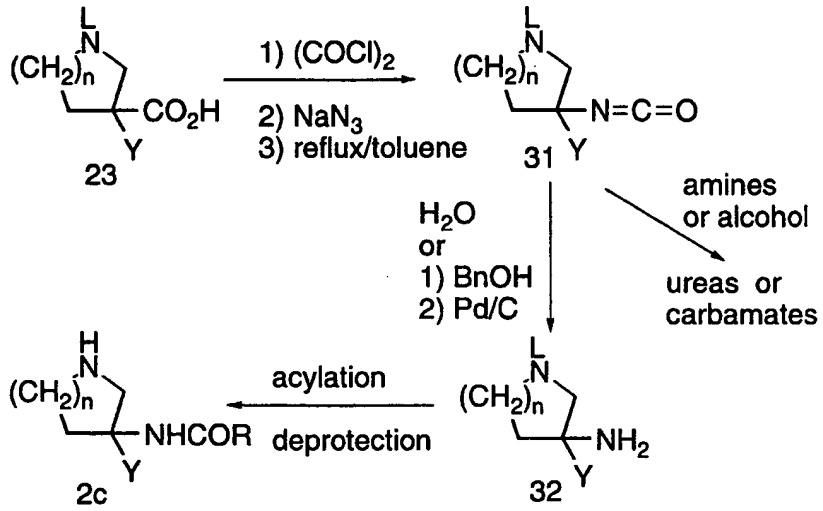
The ester in 15a may be reduced to an alcohol 18 in a suitable solvent such as THF or ether with a reducing agent such as DIBAL-H and conveniently carried out at temperatures from -100°C to 0°C. The alcohol may be acylated to Compound 19 in a suitable solvent such as dichloromethane using an acyl halide or acid anhydride in the presence of a base such as triethyl amine (TEA). The hydroxy group in 18 may also be converted to a good leaving group such as mesylate and displaced by a nucleophile such as cyanide, a thiol or an azide. Reduction of the azide in compounds of Formula 20 to an amine 21 can be achieved by hydrogenation in the presence of a noble metal such as palladium or its oxide or Raney nickel in a protic solvent such as ethanol. The nitrile can be reduced to afford the homologous amine. The amine of Formula 21 may be further elaborated to amides, ureas sulfonamides as defined by X through conventional chemistry. The protecting group L may be removed through conventional chemistry.

SCHEME 16



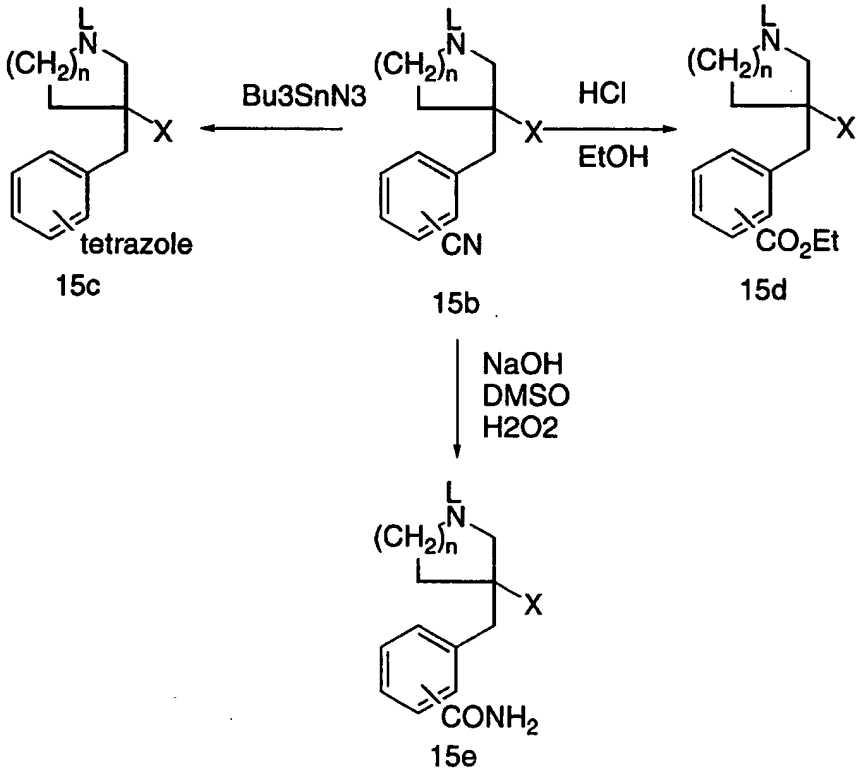
In cases where oxygen is directly attached to the ring, a convenient method involves the addition reaction by an activated form of an alkyl, aryl, alkylaryl group, such as lithium reagent, Grignard reagents, and the like with a ketone of general formula 28, which is commercially available. Further derivatization of the resulting hydroxy group by acylation, sulfonylation, alkylation, and the like gives compounds as defined by Y or X through conventional chemistry. Removal of the benzyl protective group may be carried out under the usual conditions to give compounds of general formula 2b. Shown in Scheme 16 is a general example of acylations.

SCHEME 17



In cases where a nitrogen-substituted group is directly attached to the ring, a convenient method is to use the Curtius rearrangement on the acid 23 to afford the isocyanate 31. Addition of amines or alcohols give ureas or carbamates respectively which can be deprotected to remove L to give special cases of compounds of formula 2. Conversion of the isocyanate to amine by hydrolysis gives compound 32. Further derivatization of the resulting amine group by acylation, sulfonylation, alkylation, and the like to give compounds as defined by Y or X can be done through conventional chemistry. Removal of the protective group L may be carried out under the usual conditions to give compounds of general formula 2c. Shown in Scheme 17 is a general example of acylations.

SCHEME 18



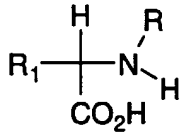
For compounds that are not readily obtainable by direct alkylation as shown in Scheme 10, modifications of easily obtainable compounds of general formula 15 may be conducted to achieve the desired substitution through conventional chemistry. For example, compounds with Y being hydroxybenzyl may be prepared by demethylation of the corresponding compound wherein Y is methoxybenzyl. Similarly, compounds with Y being aminobenzyl may be prepared by reduction of the corresponding compound wherein Y is nitrobenzyl. Shown in Scheme 18 is an example of a procedure that uses nitrile as a starting point for the preparation of compounds with different substitutions. Removal of the protective group L gives compounds of general formula 2 as described in Scheme 10.

Compounds of the general formula 2 prepared in this way are racemic when X and Y are not identical. Resolution of the two enatiomers can be conveniently achieved by classical crystallization

methods by using a chiral acid such as L- or D-tartaric acid, (+) or (-)-10-camphorsulfonic acid in a suitable solvent such as acetone, water, alcohol, ether, acetate or their mixture. Alternatively, the racemic amine 2 can be reacted with a chiral auxiliary such as (R) or (S)-O-acetylmandelic acid followed by chromatographic separation of the two diastereomers, and removal of the chiral auxiliary by hydrolysis. Alternatively asymmetric alkylation can also be utilized for the synthesis of optically active intermediate by introducing a removable chiral auxiliary in X or in place of L with subsequent chromatographic separation of diastereomers.

In cases where a sulfide is present in the molecule, it may be oxidized to a sulfoxide or to a sulfone with oxidizing agents such as sodium periodate, m-chloroperbenzoic acid or Oxone® in an solvent such as dichloromethane, alcohol or water or their mixtures.

The compounds of the present invention may also be prepared from a variety of substituted natural and unnatural amino acids of formulas 46. The preparation of many of these acids is described in US Patent No. 5,206,237. The preparation of these intermediates in racemic form is accomplished by classical methods familiar to those skilled in the art (Williams, R. M. "*Synthesis of Optically Active α-Amino Acids*" Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-



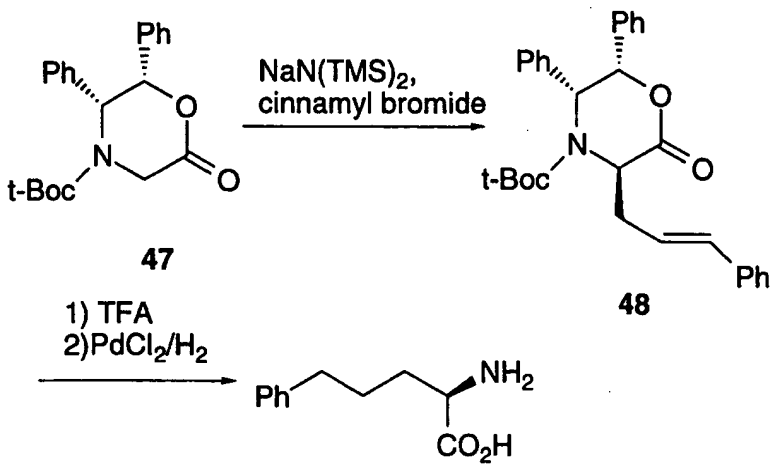
46

amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates may be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates may be converted to a

mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in *J. Am. Chem. Soc.* 1989, 111, 6354-6364.

When it is desirable to synthesize these intermediates in optically pure form, established methods include: (1) asymmetric electrophilic amination of chiral enolates (*J. Am. Chem. Soc.* 1986, 108, 6394-6395, 6395-6397, and 6397-6399), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (*J. Am. Chem. Soc.* 1992, 114, 1906; *Tetrahedron Lett.* 1987, 28, 32), (3) diastereoselective alkylation of chiral glycine enolate synthons (*J. Am. Chem. Soc.* 1991, 113, 9276; *J. Org. Chem.* 1989, 54, 3916), (4) diastereoselective nucleophilic addition to a chiral electrophilic glycinate synthon (*J. Am. Chem. Soc.* 1986, 108, 1103), (5) asymmetric hydrogenation of prochiral dehydroamino acid derivatives ("*Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D., Ed; Academic Press: Orlando, FL, 1985; Vol 5), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.* 1978, *17*, 176).

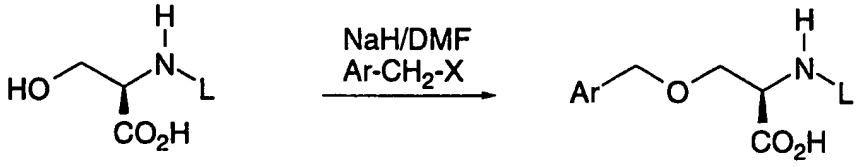
SCHEME 19



47 48 49

For example, alkylation of the enolate of diphenyloxazinone 47 (*J. Am. Chem. Soc.* 1991, 113, 9276) with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford 48 which is converted into the desired (D)-2-amino-5-phenylpentanoic acid 49 by removing the N-t-butyloxycarbonyl group with trifluoroacetic acid and hydrogenation over a $PdCl_2$ catalyst (Scheme 19).

SCHEME 20



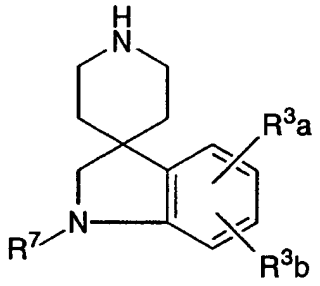
50 51

Intermediates of formula 46 which are O-benzyl-(D)-serine derivatives 51 are conveniently prepared from suitably substituted benzyl halides and N-protected-(D)-serine 50. The protecting group L is conveniently a BOC or a CBZ group. Benzylation of 64 can be achieved by a number of methods well known in the literature including deprotonation with two equivalents of sodium hydride in an inert solvent

such as DMF followed by treatment with one equivalent of a variety of benzyl halides (*Synthesis* 1989, 36) as shown in Scheme 20.

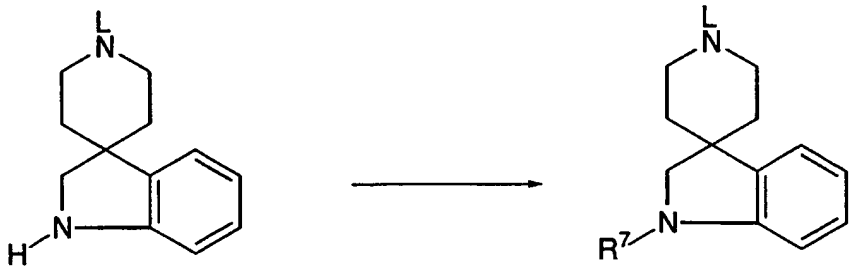
The O-alkyl-(D)-serine derivatives may also be prepared using an alkylation protocol. Other methods that could be utilized to prepare (D)-serine derivatives of formula 51 include the acid catalyzed benzylation of carboxyl protected intermediates derived from 50 with reagents of formula $ArCH_2OC(=NH)CCl_3$ (O. Yonemitsu et al., *Chem. Pharm. Bull.* 1988, 36, 4244). Alternatively, alkylation of the chiral gylcine enolates (*J. Am. Chem. Soc.* 1991, *113*, 9276; *J. Org. Chem.* 1989, *54*, 3916) with $ArCH_2OCH_2X$ where X is a leaving group affords 51. In addition D,L-O-aryl(alkyl)serines may be prepared and resolved by methods described above.

The spiro piperidines of formula 52 may be prepared by a number of methods, including the syntheses described below.



52

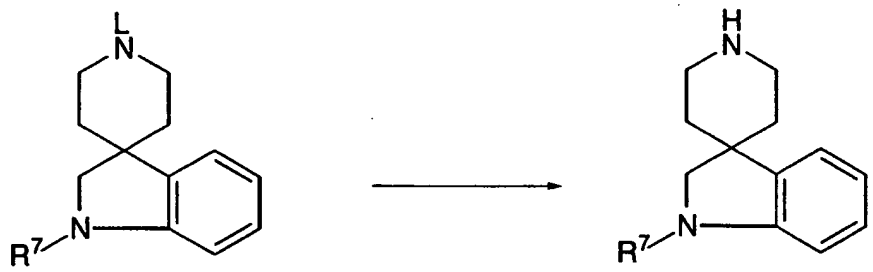
SCHEME 21



53 54

As shown in Scheme 21, the spiropiperidine of formula 43, wherein L is a defined protecting group, is synthesized by methods that are known in the literature (for example H. Ong et al *J. Med. Chem.* 1983, *23,* 981-986). The indoline nitrogen of 54, wherein L is a protecting group such as methyl or benzyl, can be reacted by with a variety of electrophiles to yield spiro piperidines of formula 54, wherein R9 can be a variety of functionalities. Compound 54 can be reacted with, for example, isocyanates in an inert solvent like dichloromethane to yield urea derivatives, chloroformates in an inert solvent such as dichloromethane to yield carbamates, acid chlorides, anhydrides, or acyl imidazoles to generate amides, sulfonyl chlorides to generate sulfonamides, sulfamyl chlorides to yield sulfamides. Also, the indoline nitrogen of 53 can be reductively alkylated with aldehydes with conditions known in the art. When the aldehyde used in the reductive amination reaction is a protected glyoxylic acid of structure HCOCOOM, wherein M is a defined protecting group, M can be removed from the product and further derivatized. Alternatively, 53 can be reacted with epoxides to produce 53, wherein R^9 is β-hydroxy-substituted alkyl or arylalkyl groups. The indoline 53 can also be transformed to compounds of formula 54, wherein R^9 = phenyl or substituted phenyl, heteroaryl or substituted heteroaryl, by carrying out the reacting 53 with a fluoro phenyl or fluoro heteroaryl reagent. This chemistry is detailed by H. Ong et al *J. Med. Chem.* 1983, *23,* 981-986.

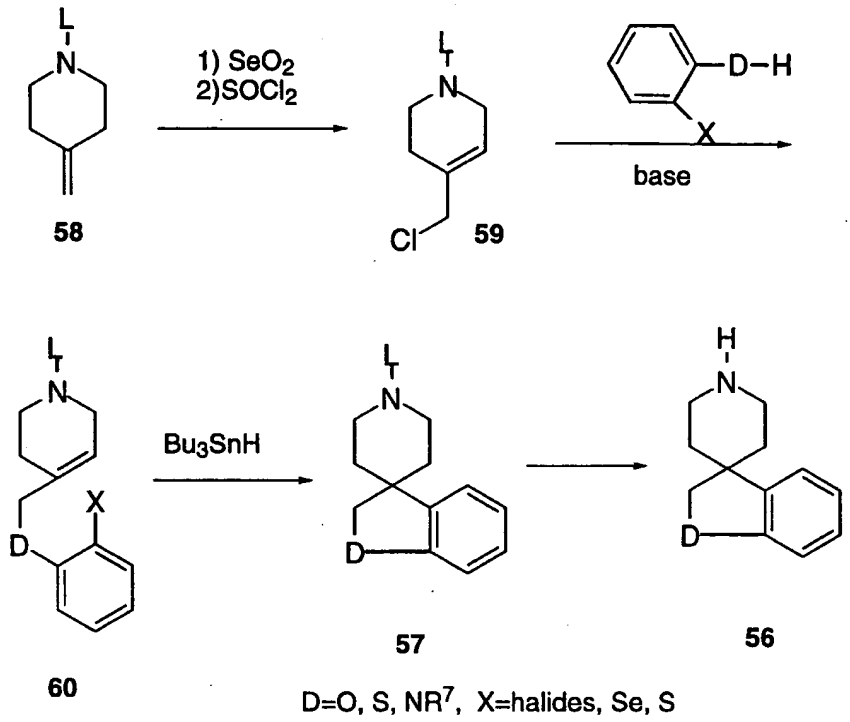
SCHEME 22



54 55

The spiro piperidine intermediate 54 (L = Me or Bn), wherein R^7 is hydrogen or most of the derivatives described above, can be demethylated or debenzylated to produce 55, wherein R^9 is hydrogen or most of the derivatives described above, as shown in Scheme 22. For compounds of formula 54, wherein L = Me, demethylation can be carried out by a number methods familiar those skilled in the art. For example, demethylation of 54 be accomplished by reacting it with cyanogen bromide and potassium carbonate in an inert solvent solvent such as dichloromethane to yield a cyanamide which can reduced to give 55 by treatment with lithium aluminum hydride in refluxing tetrahydrofuran, refluxing strong acid like aqueous hydrochloric acid, or with Grignard reagents like methyl magnesium bromide. Alternatively, demethylation of 54 can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* 1984, *49*, 2795 and references therein. For intermediates of formula 54, wherein L = Bn, removal of benzyl group can be accomplished by reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent like methanol. Alternatively, debenzylation of 54, L = Bn, can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* 1984, *49*, 2795 and references therein.

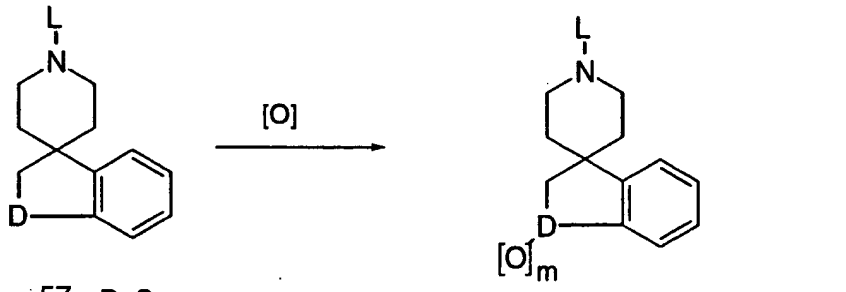
SCHEME 23



The spiro heterocyclic compounds of formula 56 can be prepared by a number of methods, including the syntheses as described in Scheme 23. Allylic oxidation of the protected piperidine 58 is accomplished by classical methods familiar to those skilled in the art (Rabjohn, N. *Org. React.* 1976, *24*, 261). The resulting allylic alcohol is treated with thionyl chloride in an inert solvent such as benzene to provide the corresponding chloride 59. When D=O or S, the alkylation is carried out in DMF or acetone as solvent with potassium carbonate as a base, and when D=NR^7 (R^7=H, alkyl, aryl, acyl, sulfonyl, carbamate) the reaction is carried out with sodium hydride as a base in an inert solvent such as THF to afford the cyclization precursor 60. When L is a defined protecting group, compound 60 can be cyclized by a number methods familiar to those skilled in the art. For example, cyclization of 60 can be accomplished by reaction with tributyltin hydride (Curran , D. P. *Synthesis* 1988, 417 and 489) in an inert solvent such as benzene to yield

57. Alternatively, compound 57 (D=NR9) can be prepared by the method shown in Schemes 24 and 25.

SCHEME 24



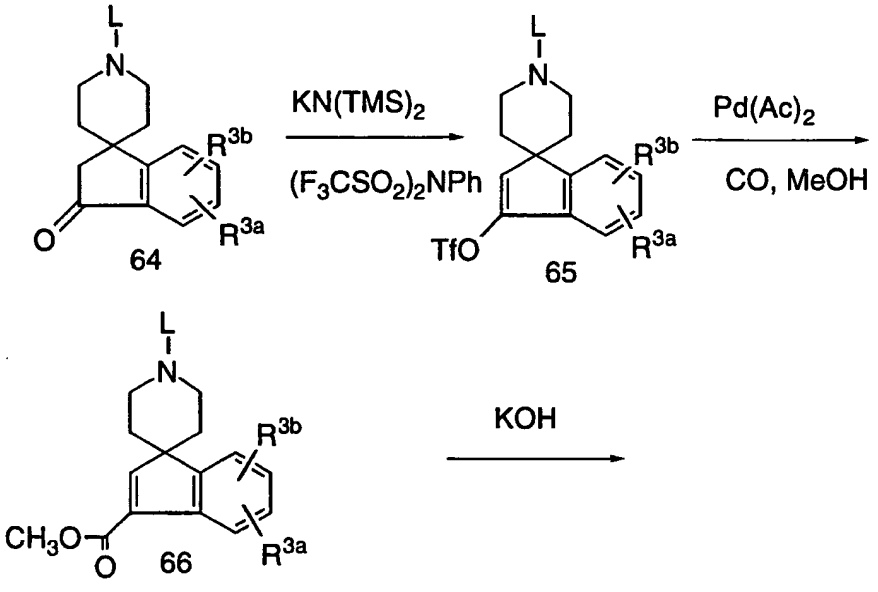
57 D=S

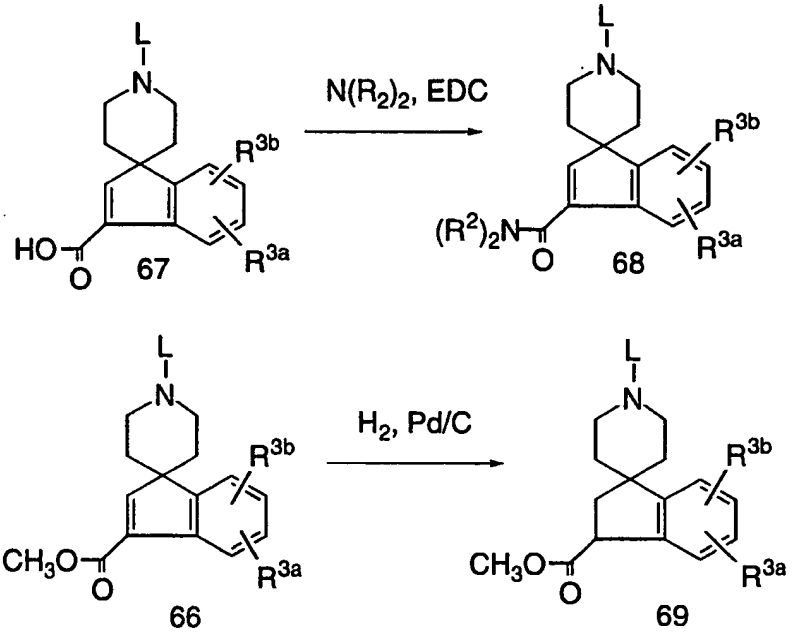
57 D = S(O)$_m$ m=1,2

As shown in Scheme 24, when D=S, compound 57 can be oxidized to the sulfoxide 57 (n=1) and the sulfone 57 (n=2) by many oxidizing agents. For example, sodium periodate is often used for the synthesis of sulfoxides and Oxone is used for the synthesis of sulfones. Removal of the protecting group provides the amine 56 which then can be incorporated into a growth hormone secretagogue via the chemistry detaileds in Scheme 1 and 8 shown above which utilize generic intermediate 2.

Compounds of formula I wherein R^4 and R^5 are each hydrogen can be further elaborated by reductive alkylation with an aldehyde by the aforementioned procedures or by alkylations such as by reaction with various epoxides. The products, obtained as hydrochloride or trifluoroacetate salts, are conveniently purified by reverse phase high performance liquid chromatogrphy (HPLC) or by recrystallization.

SCHEME 26





Homologation of the spiroindanone 64 provides easy access to spiroindanyl intermediates containing acid and ester groups. This chemistry is described in Scheme 26. Treatment of 64 with a base in an inert solvent such as THF followed by the addition of a triflating agent provides the enol triflate. Carboxylation of the enol triflate according to the procedure of Cacchi, S. Tetrahedron Letters, 1985, 1109-1112 provides the ester 66. The protecting group can then be removed as described above and the resulting amine can be incorporated into the subject compound via the chemistry depicted in Schemes 1 and 8. A compound containing an acid function is readily available via saponification of the ester group as the final step of the synthesis .

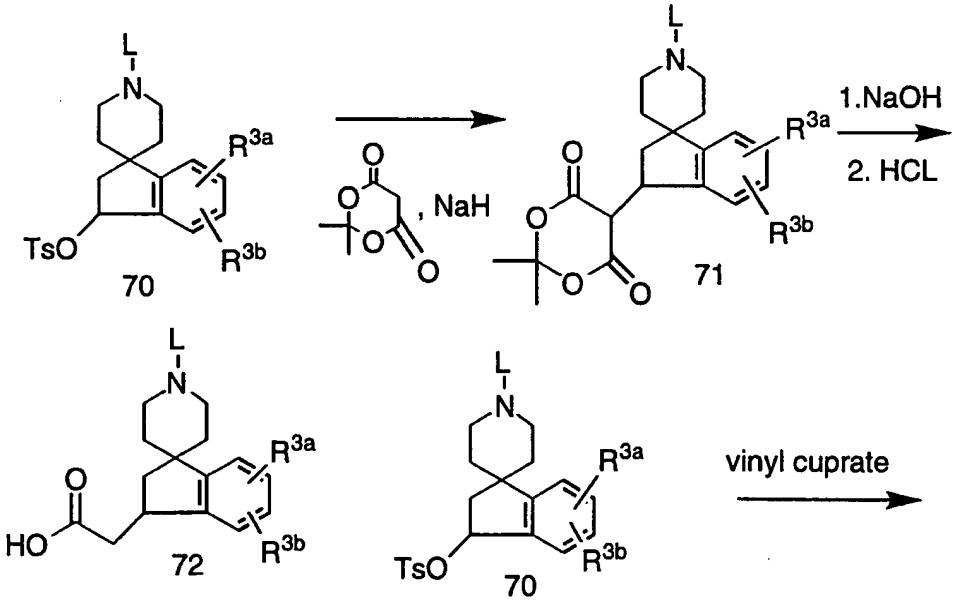
Saponification of the ester of 66 provides an acid which can be conveniently derivatized as for example reaction with an amine in the presence of a coupling agent such as EDC gives amides which can then be incorporated into final compounds following the chemistry detailed in Schemes 1 and 8.

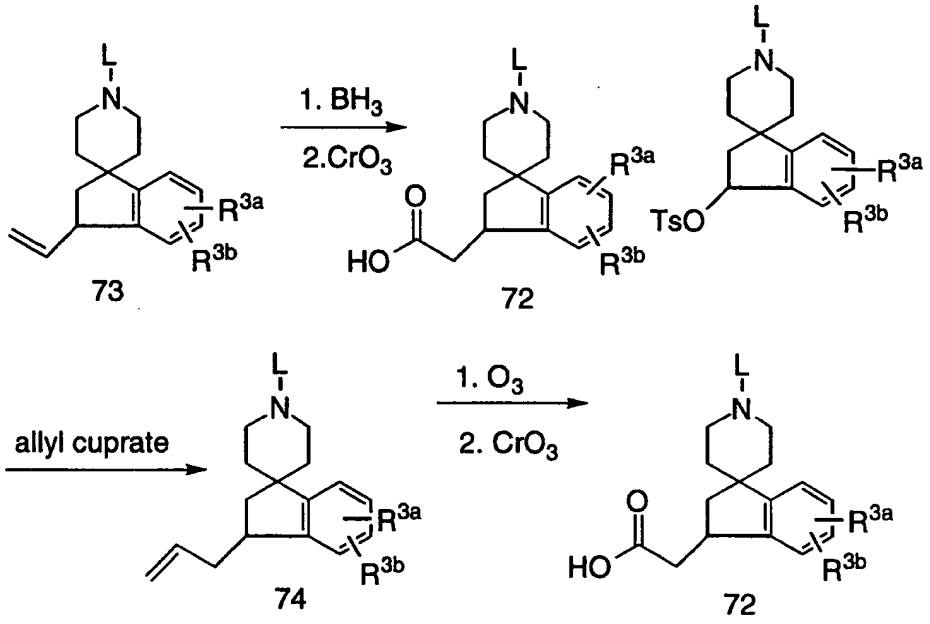
Hydrogenation of 66 using a palladium catalyst in an inert solvent provides the saturated compounds which can then either be derivatized as above or carried on to the final products via the chemistry

described in Schemes 1 and 8. The ester may also be reduced to a primary alcohol with LAH and to a aldehyde with DIBALH. Reductive alkylation of the aldehyde with ammonium acetate and sodium cyanoborohydride affords an amino methyl analog. These hydroxymethyl and aminomethyl analogs may then be further reacted to afford additional growth hormone secretagogues of the general formula I. Chiral acids are available by a variety of methods known to those skilled in the art including asymmetric catalytic hydrogenation and resolution of a pair of diastereomeric salts formed by reaction with a chiral amine such as D or L α-methylbenzylamine. The absolute stereochemistry can be determined in a number of ways including X-ray crystallography of a suitable crystalline derivative.

Spiroindane intermediates, for incorporation into growth hormone secretagogues, can be further elaborated in the benzylic position by the chemistry detailed in the following schemes.

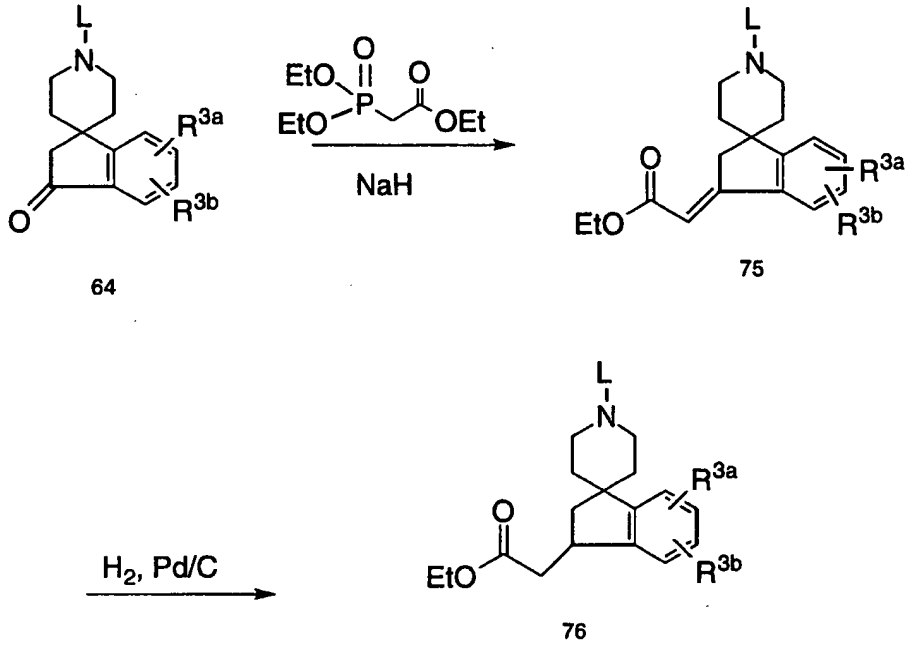
SCHEME 27





As depicted in Scheme 27, homologs of ester 69 can be conviently prepared by a variety of methods known to those skilled in the art igncluding the displacement of an activated alcohol such as tosylate 70 by a malonate nucleophile followed by decarboxylation or a cuprate reaction followed by the adjustment of the chain length or oxidation state as appropiate.

SCHEME 28



Alternatively the reaction of spiroindanone 64 with Wittig or Emmons reagents also provides access to homologs of ester 69. The chemistry is described in Scheme 28. Treatment of triethylphosphonoacetate with a base in an inert solvent such as THF followed by the addition of ketone 64 provides the unsaturated ester 75. Hydrogenation of 75 using a palladium catalyst in an inert solvent provides the saturated ester 76. The protecting group can then be removed as described above and the resulting amine can be incorporated into a final compound via the chemistry described in Schemes 1 and 8. A secretagogue containing an acid function can be obtained via saponification of the ester function as the final step of the synthesis.

Chiral esters and acids are available by a variety of methods known to those skilled in the art including asymmetric catalytic hydrogenation, chomatographic resolution of a pair of diasteromers, and via crystallization of salts formed from chiral amines such as D or L-α-methylbenzylamine. The absolute stereochemistry can be determined in

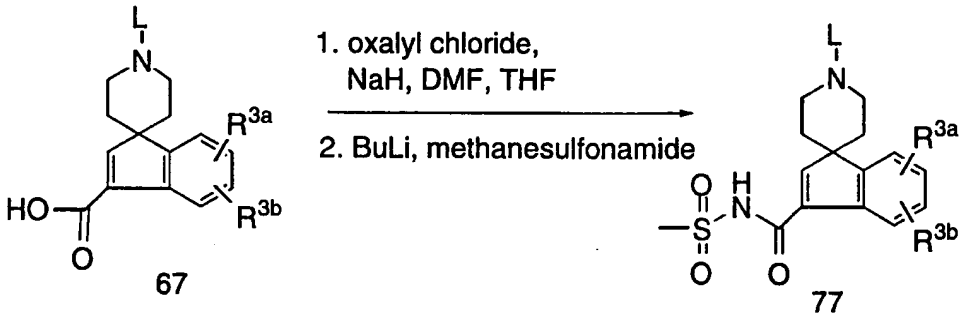
a number of ways including X-ray crystallography of a suitable crystalline derivative.

The ester can be reduced to an alcohol by treatment with LAH and to an aldehyde with DIBALH. Reductive alkylation of the aldehyde with ammonium acetate and sodium cyanoborohydride affords an amino methyl analog. These hydroxymethyl and aminomethyl analogs may then be further reacted to afford additional growth hormone secretagogues of the general formula 1.

Saponification of ester 44 provides an acid which can be conviently derivatized as for example reaction with an amine in the presence of a coupling reagent such as EDC gives amides which can be incorporated into a secretagogue as detailed in Schemes 1 and 8.

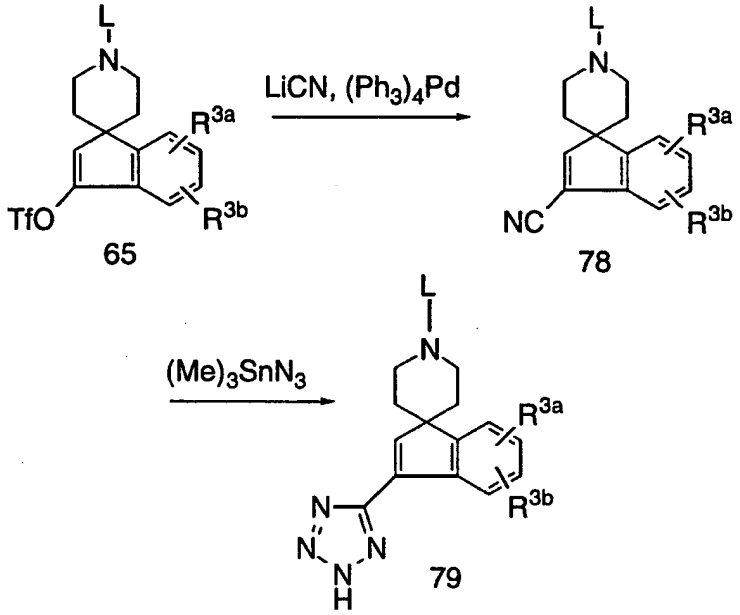
Homologation of ester 44 is possible using a variety of methods known to those skilled in the art including the method described in J. Org. Chem. 1992, 57 7194-7208.

SCHEME 29



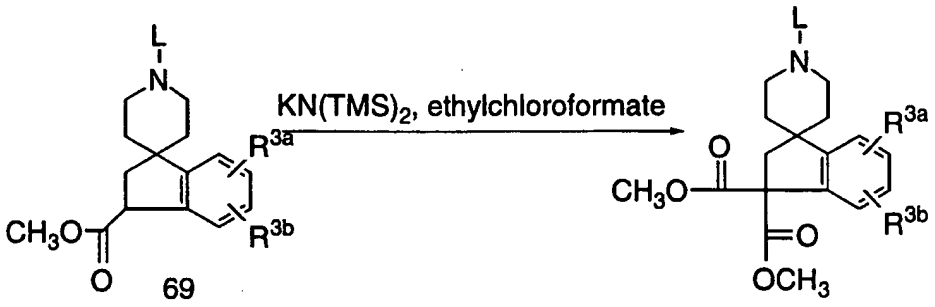
As shown in Scheme 29, a variety of acid equivalents can also be incorporated into the spiroindane intermediates for example acylsulfonamides are readily available from acids such as 67 and 72. Treatment of the spiroindane acid with a base in an inert solvent such as THF followed by the addition of oxalyl chloride provides an acid chloride which is then treated with a sodium salt of a sulfonamide. The protecting group can then be removed using chemistry described above and the resulting amine can be incorporated into a final compound using chemistry depicted in Schemes 1 and 8.

SCHEME 30



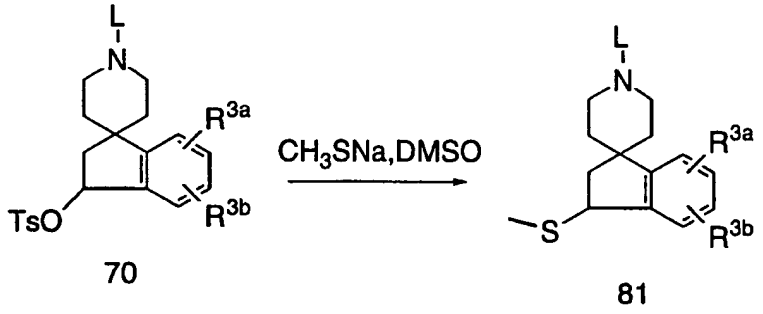
As shown in Scheme 30, tetrazole spiroindane intermediates are available from nitriles of both the shorter and longer homolog series. For example the reaction of enol triflate 65 with a cyanide anion and a palladium catalyst in the presence of an inert solvent such as toluene provides the unsaturated nitrile which can be converted into the tetrazole by reaction with trimethylstannyl azide in an inert solvent at elevated temperatures. Reduction of the indene double bond in 78 and 79 with catalysts such as Pd/C in ethanol affords the corresponding saturated analogs.

SCHEME 31



As shown in Scheme 31, esters such as 69 can be conviently acylated or alkylated next to the ester function by treatment with a variety of bases and alkylating or acylating agents. For example reaction of 69 with potassium bis(trimethyl-silylamide) in an inert solvent such as THF followed by the addition of ethyl chloroformate provides 80 in good yield. Removal of the protecting group and incorporation into the subject compounds can be accomplished as described above.

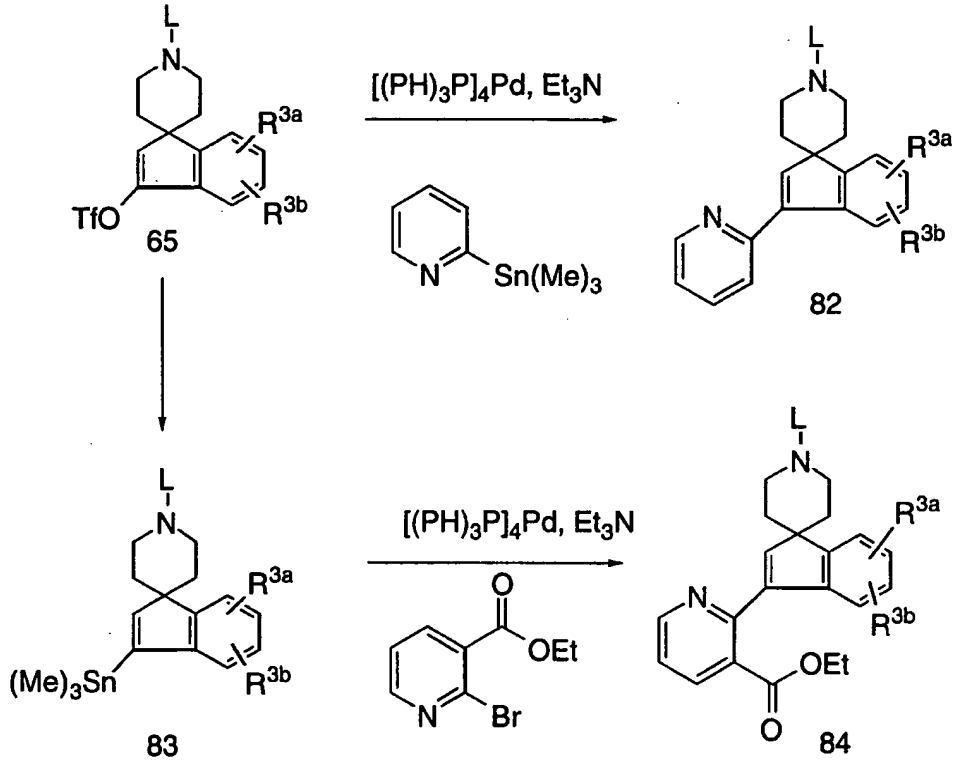
SCHEME 32



As shown in Scheme 32, further substitution at the benzylic position of the spiroindanes is readily carried out via the tosylate of the alcohol. Displacement of the tosylate with a variety of nucleophiles is possible. For example treatment of tosylate 70 with sodium thiomethoxide in DMSO provides the sulfide 81. The protecting group can be removed as above and the resulting amine can be incorporated into

the final compound employing chemistry described in Schemes 1 and 8. Alternatively the sulfide can be oxidized to the sulfoxide or sulfone by treatment with the appropriate oxidizing agent prior to deprotection or as the final step in the synthesis.

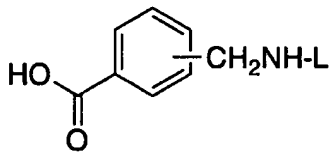
SCHEME 33



As shown in Scheme 33, the incorporation of aryl and heteroaryl groups into the benzylic position of spiroindanes is most coveniently carried out via the enol triflate 65. Palladium catalysed reaction of the enol triflate with a variety of aryl or heteroarylstannanes in an inert solvent such as toluene provides the desired intermediates. For example 2-trimethylstannyl-pyridine reacts with 65 in the presence of a catalytic amount of tetrakis(triphenylphosphene)palladium in toluene at refux to give the coupled product 82. Alternativiely the enol triflate 65 can be converted into the vinyl stannane 83 by reaction with hexamethylditin and a palladium catalyst in an inert solvent such as

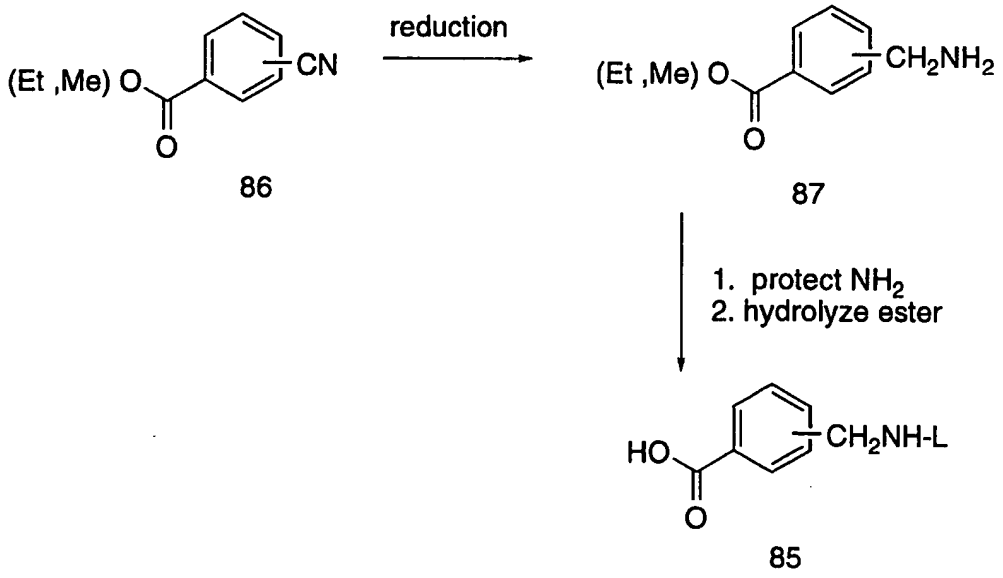
toluene. The vinyl stannane can then be coupled with a variety of aryl or hetero aryl bromides or triflates, for example coupling to 2-bromo-3-carbo-methoxypyridine provides 84. The protecting group L can be removed from the coupled products using chemistry described above and the resulting amine can be included in the final compound as described in Schemes 1 and 8.

In the following Schemes 34-36 syntheses of amino acids of Formula 6 are described. Various methods are well documented in the art to prepare protected amino acids of formula 85.



85

SCHEME 34

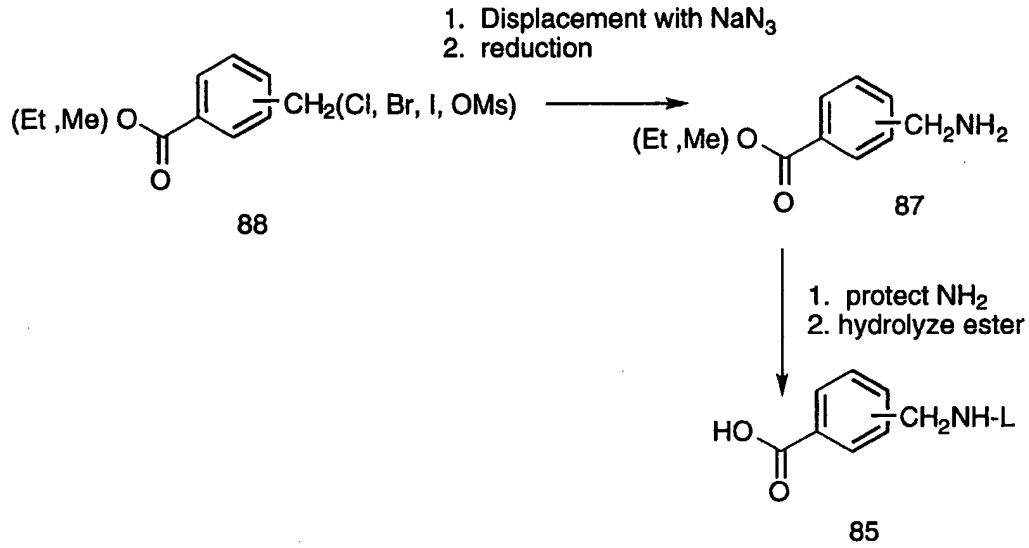


86 87 85

As shown in Scheme 34, benzoic acids esters of formula 86 are reduced with Raney nickel in ethanol in the presence of ammonia to provide the corresponding benzylamine derivative 87. The amino group

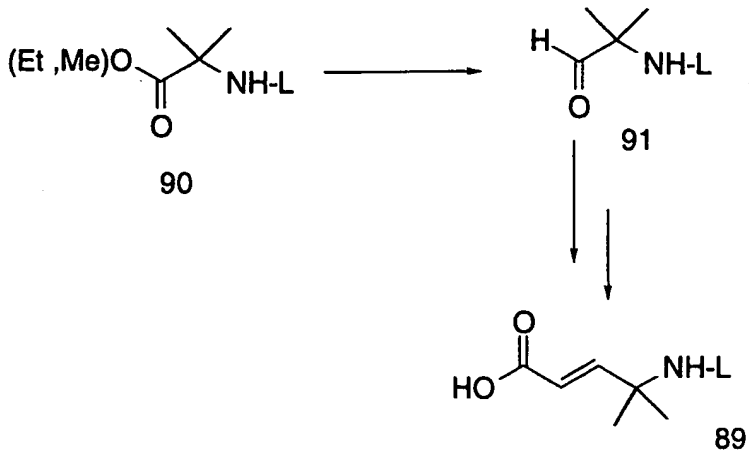
is protected as its Boc or CBZ derivative and the ester group is hydrolyzed to give protected amino acids of formula 85.

SCHEME 35



As shown in Scheme 35, other methods of the synthesis of 85 originate from benzyl halides of formula 88. The halide is displaced with sodium azide usually in a polar aprotic solvent such as DMF or DMSO to give the corresponding azide that is reduced with triphenylphosphine in THF-water to give the amine derivative that is converted to acids of formula 85 as described above.

SCHEME 36



Olefinic amino acids of formula 89 may be prepared as shown in Scheme 36. The Boc-aminoisobutyric acid methyl ester 90 is reduced to the corresponding aldehyde derivative 91 with the use of diisobutylaluminum hydride in a aprotic solvent such as THF or dichloromethane. Alternatively, the commercially available acid of 90 may be reduced with diborane to the alcohol and reduced up to the aldehyde 91 by using Swern oxidation protocol. A Horner-Emmons condensation of 91 with triethylphosphonoacetate by using a base like potassium t-butoxide in an aprotic solvent provides the corresponding unsaturated aester that can be hydrolyzed under standard conditions to protected amino acid of formula 89.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

The utility of the compounds of the present invention as growth hormone secretagogues may be demonstrated by methodology known in the art, such as an assay disclosed by Smith , et al., Science, 260, 1640-1643 (1993) (see text of Figure 2 therein). In particular, all of the compounds prepared in the following examples had activity as growth hormone secretagogues in the aforementioned assay. Such a result is indicative of the intrinsic activity of the present compounds as growth hormone secretagogues.

The growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release. Other hormones that are important and in need of study as to their effect on growth hormone release include the gonadal hormones, e.g., testosterone, estradiol, and progesterone; the adrenal hormones, e.g., cortisol and other corticoids, epinephrine and norepinephrine; the pancreatic and gastrointestinal hormones, e.g., insulin, glucagon, gastrin, secretin; the vasoactive peptides, e.g., bombesin, the neurokinins; and the thyroid hormones, e.g., thyroxine and triiodothyronine. The compounds of Formula I can also be employed to investigate the possible negative or positive feedback effects of some of the pituitary hormones, e.g., growth hormone and endorphin peptides, on the pituitary to modify growth hormone release. Of particular scientific importance is the use of these compounds to elucidate the subcellular mechanisms mediating the release of growth hormone.

The compounds of Formula I can be administered to animals, including man, to release growth hormone *in vivo*. For example, the compounds can be administered to commercially important animals such as swine, cattle, sheep and the like to accelerate and increase their rate and extent of growth, to improve feed efficiency and to increase milk production in such animals. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly

determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutical carrier or diluent. Optionally, the active ingredient of the pharmaceutical compositions can comprise an anabolic agent in addition to at least one of the compounds of Formula I or another composition which exhibits a different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or in combination with a corticosteroid to minimize the latter's catabolic side effects or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH, diethylstilbesterol, amino acids, estrogens, β-agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, retinoic acid, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox. or peptides disclosed in U.S. Patent No. 4,411,890.

A still further use of the compounds of this invention is in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6, GHRP-1 as described in U.S. Patent Nos. 4,411,890 and publications WO 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or α-adrenergic agonists such as clonidine or serotonin 5HTID agonists such as sumitriptan or agents which inhibit somatostatin or its release such as physostigmine and pyridostigmine. In particular, the compounds of this invention may be used in combination with growth hormone releasing factor, an analog of growth hormone releasing factor, IGF-1, or IGF-2. For example, a compound of the present invention may be used in combination with IGF-1 for the treatment or prevention of obesity. In addition, a

compound of this invention may be employed in conjunction with retinoic acid to improve the condition of musculature and skin that results from intrinsic aging.

The present invention is further directed to a method for the manufacture of a medicament for stimulating the release of growth hormone in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

As is well known to those skilled in the art, the known and potential uses of growth hormone are varied and multitudinous. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses may be summarized as follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; prevention of catabolic side effects of glucocorticoids; treatment of osteoporosis; stimulation of the immune system, acceleration of wound healing; accelerating bone fracture repair; treatment of growth retardation; treating acute or chronic renal failure or insufficiency; treatment of physiological short stature, including growth hormone deficient children; treating short stature associated with chronic illness; treating obesity and growth retardation associated with obesity; treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treatment of intrauterine growth retardation, and skeletal dysplasia; treatment of hypercortisonism and Cushing's syndrome; treatment of peripheral neuropathies; replacement of growth hormone in stressed patients; treatment of osteochondrodysplasias, Noonans syndrome, sleep disorders, schizophrenia, depression, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treatment of pulmonary dysfunction and ventilator dependency; prevention or treatment of congestive heart failure, improving pulmonary function, restoring systolic and diastolic function, increasing myocardial contractility, decreasing peripheral total vascular resistance, diminishing or preventing loss of body weight and enhancing

recovery following congestive heart failure; increasing appetite; attenuation of protein catabolic response after a major operation; treating malabsorption syndromes; reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treatment of hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; stimulation of thymic development and preventtion of the age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treatment of immunosuppressed patients and to enhance antibody response following vaccination; increasing the total lymphocyte count of a human, in particular, increasing the T4/T8-cell ratio in a human with a depressed T4/T8-cell ratio resulting, for example, from infection, such as bacterial or viral infection, especially infection with the human immunodeficiency virus; treatment of syndromes manifested by non-restorative sleep and musculoskeletal pain, including fibromyalgia syndrome or chronic fatigue syndrome; improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulation of osteoblasts, bone remodelling, and cartilage growth; prevention and treatment of congestive heart failure; protection of cardiac structure and/or cardiac function; enhancing of recovery of a mammal following congestive heart failure; enhancing and/or improving sleep quality as well as the prevention and treatment of sleep disturbances; enhancing or improving sleep quality by increasing sleep efficiency and augmenting sleep maintenance; prevention and treatment of mood disorders, in particular depression; improving mood and subjective well being in a subject suffering from depression; stimulation of the immune system in companion animals and treatment of disorders of aging in companion animals; growth promotant in livestock; and stimulation of wool growth in sheep. Further, the instant compounds are useful for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock. Likewise, the instant compounds are useful in a method of treatment of diseases or conditions which are

benefited by the anabolic effects of enhanced growth hormone levels that comprises the administration of an instant compound.

In particular, the instant compounds are useful in the prevention or treatment of a condition selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; bone fracture, including hip fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; short stature in children; obesity; sleep disorders; cachexia and protein loss due to chronic illness such as AIDS or cancer; and treating patients recovering from major surgery, wounds or burns, in a patient in need thereof.

In addition, the instant compounds may be useful in the treatment of illnesses induced or facilitated by corticotropin releasing factor or stress- and anxiety-related disorders, including stress-induced depression and headache, abdominal bowel syndrome, immune suppression, HIV infections, Alzheimer's disease, gastrointestinal disease, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, and fertility problems.

It will be known to those skilled on the art that there are numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents some of which have also been mentioned above with the growth hormone secretagogues of this invention will bring additional, complementary, and often synergistic properties to enhance the growth promotant, anabolic and desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently present in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly.

Combined therapy to inhibit bone resorption, prevent osteoporosis and enhance the healing of bone fractures can be illustrated by combinations of bisphosphonates and the growth hormone secretagogues of this invention. The use of bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T. Role of

Bisphosphonates in Metabolic Bone Diseases. *Trends in Endocrinol. Metab.*, , *4*, 19-25 (1993). Bisphosphonates with these utilities include alendronate, tiludronate, dimethyl - APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995. According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

In the case of alendronate daily oral dosage levels of 0.1 mg to 50 mg are combined for effective osteoporosis therapy with 0.01 mg/kg to 20 mg/kg of the growth hormone secretagogues of this invention.

Osteoporosis and other bone disorders may also be treated with compounds of this invention in combination with calcitonin, estrogens, raloxifene and calcium supplements such as calcium citrate or calcium carbonate.

Anabolic effects especially in the treatment of geriatric male patients are obtained with compounds of this invention in combination with anabolic steroids such as oxymetholone, methyltesterone, fluoxymesterone and stanozolol.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated in dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

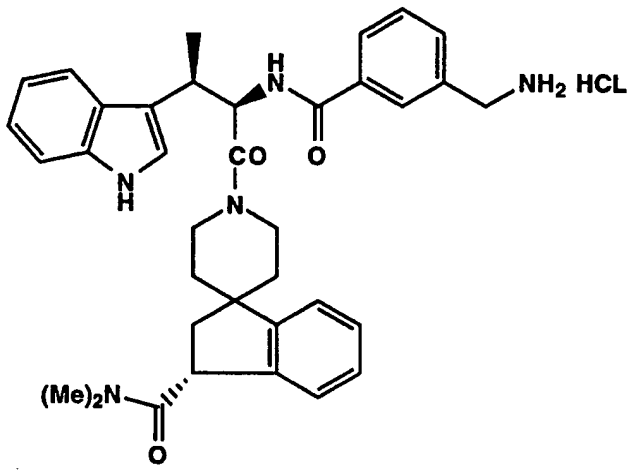
Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 10 mg/kg. of body weight daily are administered to patients and animals, e.g., mammals, to obtain effective release of growth hormone. Preferably, the dosage level will be about 0.001 to about 25 mg/kg per day; more preferably about 0.01 to about 10 mg/kg per day.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

EXAMPLE 1



Step A: N-Acetyl-*Threo*-(2R,3S)-β-methyltryptophan R-(+)-α-methylbenzyl amine salt

Racemic β-methyltryptophan was prepared by the method of Snyder and Matteson (*J. Am. Chem. Soc.* 1957, 79, 2217.) Isomer A (100g) was suspended in 1.25L of 90/10 acetone water at 20°C and 50 mL of R-(+)-α-methylbenzylamine was added in one portion. The suspension cleared briefly before a thick white suspension formed which quickly turned to a solid mass. After aging overnight, an additional 500 mL of acetone was added to facilitate agitation and filtration. The suspension was filtered and the cake washed with 500 mL of acetone and sucked to a damp cake. The solid was suspended in 2.5 L of 90/10 acetone /water and heated to boiling on a steam bath. The white slurry was allowed to cool to 20°C overnight. The product was collected by filtration, washed with acetone and dried yielding 39.1 g of the title compound. $\alpha = +9.1^{\circ}$ (c=1, MeOH) Stereochemical assignments were

made by comparison to published compounds: *J. Org. Chem.* 1994, 59, 4239 and *J. Org. Chem.* 1995, 60, 4978.

Step B: N-Acetyl-*Threo*-(2S,3R)-β-methyltryptophan S-(-)-α-methylbenzyl amine salt

The mother liquors from the Step A were combined and concentrated to *ca.* 1 L and 400 mL of 1 N HCl was added. The resulting suspension was stirred for 1 hr initially at 20°C then at 0°C. The product was filtered and washed with water until the filtrate was neutral. The product was sucked to a damp cake weighing 79 g. The solid was suspended in 1L of 95% acetone/water and 40 mL of S-(-)-α-methylbenzylamine was added followed by 1 L of 90% acetone/water. After a few minutes a solid mass formed. An additional 500 mL of acetone was added and the mixture heated on a steam bath for *ca.* 0.5 hr. This was then allowed to stand at 20°C overnight. The product was collected by filtration, washed with 500 mL of acetone, and sucked to a damp cake. The product was suspended in 2 L of 95% acetone/water and heated on a steam bath to boiling. The white suspension was allowed to cool to 20°C overnight. The product was collected by filtration, washed with 500 mL of acetone and dried yielding 54 g. $\alpha = -9.0^{o}$ (c=1, MeOH).

Step C: N-Acetyl-*Erythro* (2R,3R)-β-methyltryptophan R-(+)-α-methylbenzyl amine salt

170g of Isomer B (see ref. in Step A) which was a brittle foam containing ethyl acetate was dissolved in 2.5 L of ethyl acetate containing 100 mL of ethanol. To this was added 60 mL of R-(+)-α-methylbenzylamine. After 10 min, an additional 2L of ethyl acetate was added and the resulting thick suspension was aged at 20°C for 3 days. The product was collected by filtration, washed with ethyl acetate and and sucked to a damp cake. The salt was reslurried four times with hot ethyl acetate containing 2% water (1 x 2.5 L, 2 x 6 L, and 1 x 8 L). The yield of dried product was 43.2 g of salt. $\alpha = -19.6^{o}$ (c=1, MeOH).

Step D: N-Acetyl-*Erythro* (2S,3S)-β-methyltryptophan S-(-)-α-methylbenzyl amine salt

The mother liquors from the Step C were combined and concentrated to *ca.* 2 L and washed twice with 500 mL 1 N HCl. The washes were back extracted once with ethyl acatate, and the combined ethyl acetate extracts washed twice with brine. The solution was diluted to 6 L with ethyl acatate and 60 mL of S-(-)-α-methylbenzylamine was added. After 10 min the resulting suspension was heated to boiling. The suspension was allowed to cool to ambient temperature with stirring overnight. The product was collected by filtration washed with ethyl acetate and and sucked to a damp cake. The salt was suspended in 6 L of ethyl acetate and suspension was heated to boiling. The suspension was allowed to cool to ambient temperature with stirring overnight. The product was collected by filtration washed with ethyl acetate and dried. The yield of dried product was 65.8 g of salt. $\alpha = +19.7^{o}$ (c=1, MeOH).

Step E: N-acetyl-*threo*-(2S,3R)-β-Methyltryptophan

The salt from Step B (53 g) was stirred with 400 mL 1 N HCl at 20°C for 20 min. The suspension was filtered and the cake washed with water until the filtrate was neutral. The wet cake was used directly for the next reaction. A sample was dried affording the title compound. $\alpha = -26.4^{o}$ (c=1,MeOH).

Step F: *threo*-(2S,3R)-β-Methyltryptophan

The wet cake from Step E was suspended in with 400 mL of 1 N HCl and refluxed for 12 hours. The solution was cooled to 20°C, and half of the solution was used for Step G. The title compound isolated by adjusting the pH to 7.0 with sodium hydroxide, cooling the resulting suspension to 0°C, filtering, washing the cake with water and drying. $\alpha = -29.3^{o}$ (c=0.9, H_2O).

Step G: N-*t*-BOC-*threo*-(2S,3R)-β-methyltryptophan

The pH of the aqueous solution from Step F was adjusted to 7 with sodium hydroxide and cooled to 0°C. 20 g of potassium

carbonate, 19 g of di-t-butyldicarbonate, and 150 mL of THF were added. The mixture was allowed to warm slowly to ambient temperature overnight. The reaction was extracted twice with ether, the aqueous acidified with 2 N HCl and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried with $MgSO_4$, filtered and concentrated affording 21.2 g of the title compound.

Step H: N-Acetyl-*threo*-(2R,3S)-β-methyltryptophan

The title compound was prepared following the procedure of Step E. $\alpha = +26.6^{o}$ (c=1,MeOH).

Step I: *threo*-(2R,3S)-β-Methyltryptophan

The title compound was prepared following the procedure of Step F. $\alpha = +30.6^{o}$ (c=0.9, H_2O).

Step J: N-*t*-BOC-*threo*-(2R,3S)-β-Methyltryptophan

The title compound was prepared following the procedure of Step G.

Step K: N-Acetyl-*Erythro* (2S,3S)-β-methyltryptophan

The salt from GRK example 4 (65 g) was stirred with 250 mL 1 N HCl and 1.5 L of ethyl acetate at ambient temperature for 5 min. The layers were partitioned and the ethyl acetate layer was washed with 1N HCl, H_2O and brine, dried with $MgSO_4$, filtered and concentrated to afford the title compound as a brittle foam.

Step L: *Erythro* (2S,3S)-β-methyltryptophan

The product from Step K was suspended in with 500 mL of 2 N HCl and refluxed for 4 hours. The solution was cooled to 20°C, and half of the solution was used for Step M. The title compound isolated as a foam by concentrating the solution *in vacuo*.

Step M: N-*t*-BOC-*Erythro* (2S,3S)-β-methyltryptophan

The pH of the aqueous solution from Step F was adjusted to 7 with sodium hydroxide and cooled to 0°C. 24 g of potassium carbonate, 22 g of di-t-butyldicarbonate, and 150 mL of THF were added. The mixture was allowed to warm slowly to ambient temperature overnight. The reaction was extracted twice with ether The aqueous acidified with 2 N HCl.and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried with $MgSO_4$ filtered and concentrated. The solid was redissolved in ether, and the ether removed *in vacuo* while flushing with hexanes. The resulting slurry was filtered and dried affording 20.1 g of the title compound.

Step N: N-Acetyl-*threo*-(2R,3R)-β-methyltryptophan

The title compound was prepared following the procedure of Step K. $\alpha =$ ° (c=1,MeOH).

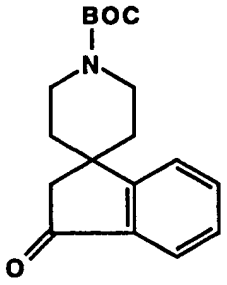
Step O: *threo*-(2R,3R)-β-methyltryptophan

The title compound was prepared following the procedure of Step L. $\alpha =$ ° (c=0.9, H_2O).

Step P: N-*t*-BOC-*threo*-(2R,3R)-β-methyltryptophan

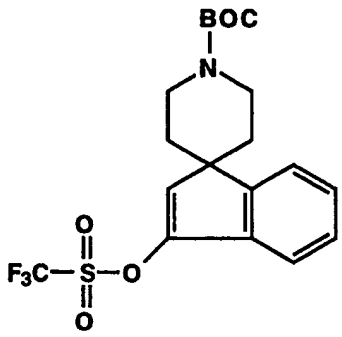
The title compound was prepared following the procedure of Step M.

Step Q:



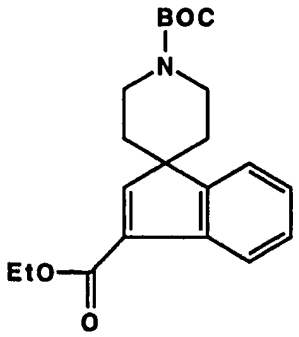
To a solution of 51.0 g (0.177 mol) of 1'-(t-butyloxy-carbonyl)spiro[1H-indene-1,4'-piperidine] [prepared by the method of Chambers, et al, J. Med. Chem. , 1992, 35, 2036] in 200 ml of THF was added 430 ml (0.5 M in THF, 0.213 mol) of 9-BBN. The reaction mixture was heated at 70°C until TLC analysis indicated that the starting material was consumed (18 hrs). The solution was concentrated to ~300 ml and then cooled to 0^0C and quenched with methanol (10 ml). 4 N Sodium hydroxide (213 ml) and 30 % hydrogen peroxide (108 ml) were added via an addition funnel over 45 minutes. The reaction mixture was stirred for 3.5 hours and then solid sodium sulfite was added until starch paper indicated that no more peroxides were present. The reaction mixture was extracted with ethyl acetate (4 X 1 vol). The ethyl acetate layer was dried over magnesium sulfate filtered and concentrated. The crude material was dissolved in dichloromethane (300 ml) and the solution was cooled to 0°C then celite (25 g) and PCC (57 g) were added in five portions over 20 minutes. The reaction mixture was warmed to room temperature and stirred overnight. The solution was then diluted with ether and filtered through a pad of a mixture of celite and florisil. Purification by flash chromotgraphy (silica gel, hexane/ethyl acetate, 5:1 to 3:1) gave 58.6 g of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): 7.75-7.60 (m, 2H), 7.50-7.44 (m, 2H), 4.30-4.15 (m, 2H), 2.85 (dt, 2H), 2.63 (s, 2H), 1.98 (dt, 2H), 1.53-1.40 (m, 2H), 1.49 (s, 9H).

Step R:



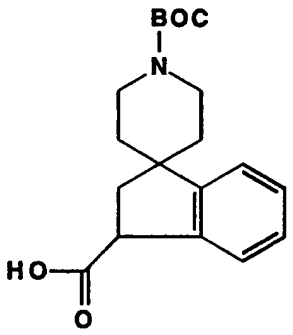
Potasium bis(trimethylsilyl)amide (127.5 ml, 0.5 M) was added to the ketone (16.0 g, 53 mmol) in THF (200 mL) at 0 ^{0}C. The reaction mixture was stirred for one hour and then N-phenyltrifluromethanesulfonamide was added. The ice bath was allowed to melt and the reaction mixture was stirred overnight at room temperature. Water was added and the aqueous layer was extracted with ethyl acetate (3 X 1 vol). The organic layer was washed with brine and then dried over magnesium sulfate, filtered and then concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 8 : 1) to give the title compound (17.8 g) as a waxy solid. ^{1}HNMR (200 MHz, $CDCl_3$): 7.65-7.14 (m, 4 H), 6.66 (s, 1 H), 4.30-4.15 (m, 2 H), 3.24-2.96 (m, 2H), 2.06 (dt, 2 H), 1.50 (s, 9 H), 1.49-1.38 (m, 2 H).

Step S:



A solution of 17.4 g of the intermediate from Step R, 11.0 ml of triethylamine, 634 mg of triphenylphosphine, and 240 mg of palladium acetate in 72 ml of ethanol and 158.0 ml of DMF was purged for 10 minutes with carbon monoxide and then stirred under a carbon monoxide atmosphere for 24 hours. The ethanol was removed in vacuum and the reaction mixture was diluted with water and extracted repeatedly with ethyl acetate. The ethyl acetate layer was washed with 1N HCl, water, and brine and then dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (hexane/ethyl acetate 8:1) provided 27.6 g of the title compound as a colorless oil. ^{1}HNMR (200 MHz, $CDCl_3$): 8.0-7.94 (m,1H), 7.7 (s, 1 H), 7.4-7.25 (m, 3H), 4.4 (q,2H), 4.25-4.15 (m, 2H), 3.13 (dt, 2H), 2.03 (dt, 2H), 1.5 (s, 9H), 1.55-1.35 (m, 2H), 1.4 (t, 3H).

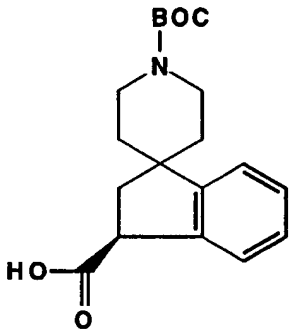
Step T:



To a suspension of Pd/C (1.7g) in ethanol (300 ml) was added the title compound (27 g) from Step S. The reaction mixture was purged with hydrogen and then shaken under a hydrogen atmosphere for 3 hours. The mixture was purged with nitrogen and filtered through celite and concentrated to give the title compound (27 g). The crude product was dissolved in ethanol (200 ml) and 2N sodium hydroxide (76 ml) was added. The reaction mixture was heated to 50 ^{0}C for three hours then cooled and the ethanol was removed under vacuum and the residue was dissloved in ethyl acetate. 1N HCl was added and the layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 1 vol). The combined organic layers were washed with saturated aqueous

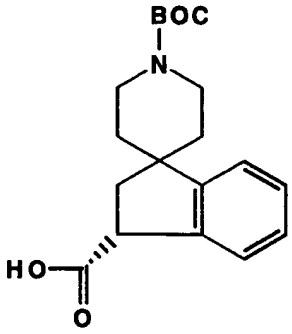
NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to provide the title compound (23.8 g) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$): 7.50-7.42 (m, 1 H), 7.34-7.12 (m, 3 H), 4.22-4.04 (m, 3 H), 3.06-2.84 (m, 2 H), 2.40 (d, 2 H), 1.88-1.6 (m, 4 H), 1.50 (s, 9 H).

Step U:



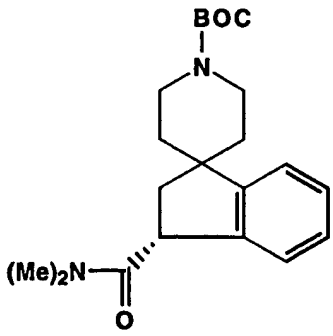
The acid from Step T (23.5 g, 0.07 mol) was dissolved in toluene (150 ml) and R- methylbenzylamine (9.02 ml) was added. The toluene solution was heated on a steam bath until everything was in solution. The solution was then seeded with crystals grown in the same way on a much smaller scale. The solution was allowed to sit overnight and then the mixture was filtered to give 15.8 g of crystals. The crystals were recrystalized from toluene two more times.The crystals (12 g) were dissolved in ethyl acetate /1 N HCl and the organic layer was washed with 1 N HCL (2 X 1 vol) and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated to give 8.9 g of the title compound. $[\alpha]^D$ = -16.9 (c= 0.84, methanol)

Step V:



The mother liqueurs from Step U were washed with 1 N HCl (2 x1 vol) and brine dried over magnesium sulfate, filtered, and concentrated to give recovered acid (15.4 g). To this acid in toluene (100 mL) was added S-methylbenzylamine (5.95 mL). The crystals were recrystallized four times from toluene as above to give 12.3 g of salt. The salt was dissolved in ethyl acetate / 1 N HCl and washed with 1 N HCl (2 X 1 vol) and brine. The organic layer was dried over magnesium sulfate and filtered and concentrated to give the title compound (9.0 g). $[\alpha]^D = +17.1$ (c= 1.06, methanol).

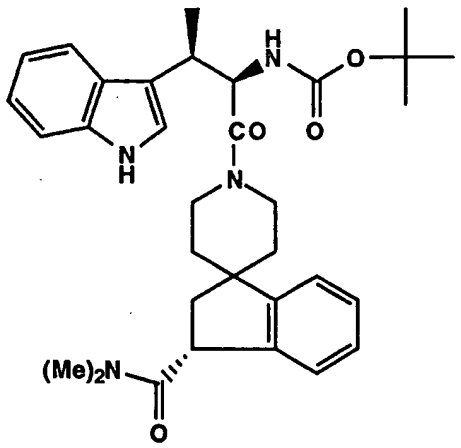
Step W:



A solution of the title compound from Step V (14.0 g, 42 mMol) in dichloromethane was cooled to 0 ^{0}C and dimethylamine (25.4 mL, 2M in THF) was added. The mixture was stirred for ten minutes at 0^{0}C and then EDC and DMAP were added. The reaction mixture was stirred for four hours at 0 ^{0}C and then quenched with 1 N HCl. The

aqueous layers were extracted with dichloromethane and the combined organic layers were then washed with water and brine and dried over sodium sulfate. The crude product was purified by flash chromatography (dichloromethane/acetone 9:1) to give the title compound (12.2 g). HPLC analysis (chiralcel OD-R, 50% 0.5N $NaClO_4$ / 50% acetonitrile, 0.5 ml/min. E_1 retention time 20.8 min (E_1 prepared from the intermediate in Example 1 Step U as in Example 1 Step W; E_2 retention time 24.7 min) showed it to be approximately a 1 : 200 mixture of enantiomers. ^{1}HNMR (400 MHz, $CDCl_3$): 7.25-7.05(m, 4 H), 4.35 (t,1 H), 4.20-4.10 (m, 2 H), 3.25 (s, 3 H), 3.05 (s, 3 H), 2.90-2.85 (m, 2H), 2.42-2.28 (m, 2H), 1.95 (dt, 1H), 1.75-1.60 (m, 2 H), 1.52-1.50 (m, 1 H), 1.49 (s, 9H).

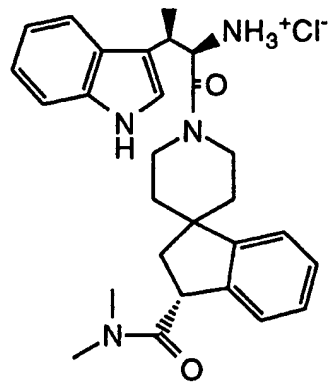
Step X:



A sample of the title compound from Example 1 Step W was deprotected with a saturated solution of HCl in ethyl acetate as above to give the hydrochoride salt (6.3 g, 21 mmol). To this salt in dichloromethane at 0^0C was added the intermediate prepared in Example ! Step P (7.0 g, 22 mmol), HOBT (4.4g, 33 mmol), NMM (4.83 ml,44 mmol) and finally EDC(6.3g, 33 mmol). The reaction mixture was warmed to room temperature and stirred overnight. It was then poured into ethyl acetate and washed with 1 N HCl, saturated bicarb, and brine then dried over magnesium sulfate. The organic layer was filtered and

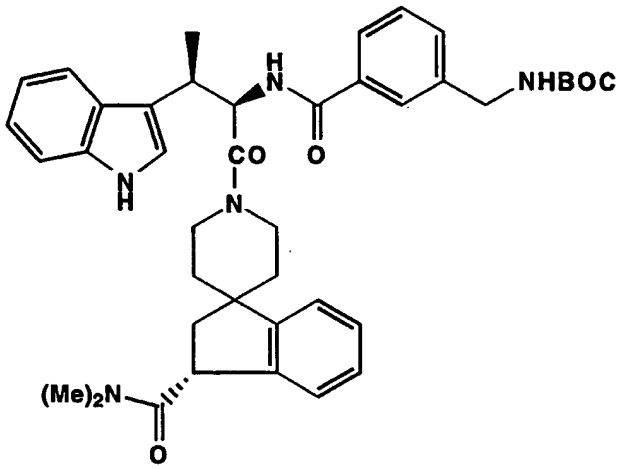
concentrated. Purification by flash chromatography (ethyl acetate) provided the title compound (10 g, 17.9 mmol).

Step Y:



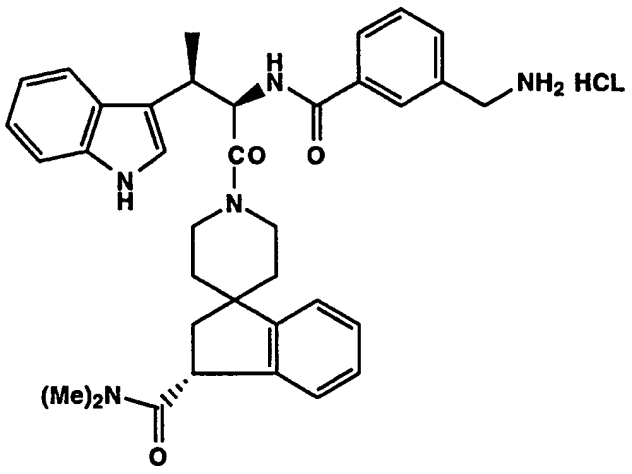
A solution of the N-Boc dipeptide from the previous step (1.32 g, 2.6 mmol)) in ethyl acetate (8 mL) was cooled to 0°C. While stirring, HCl-EtOAc was added to the mixture (10 mL). The reaction was stirred for 20 minutes, until TLC analysis indicated that the reaction was complete. The solution was then concentrated to remove the ethyl acetate to afford 1.25g of the product (100%). ESI-MS calc. for C28H33N4O2: 457; Found 458 (M+H).

Step Z:



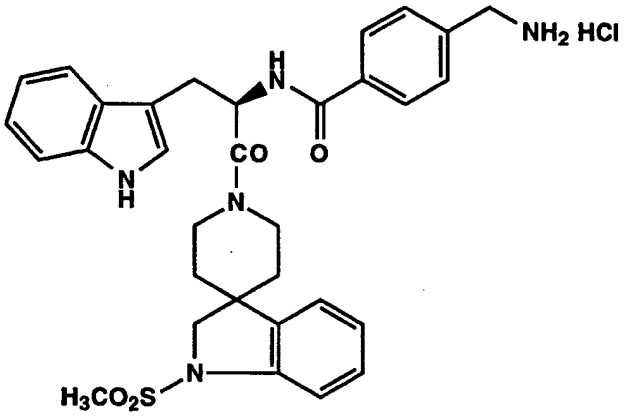
To a solution of the intermediate from the previous step in methylene chloride was added N-Boc-3-methylaminobenzoic acid (62 mg), EDC(58 mg), HOBT (41mg), and NMM (0.24ml). The reaction mixture was stirred overnight and then loaded onto a prepTLC plate. Elution with methylene chloride /acetone (8 :2) gave 79 mg .

Step AA:

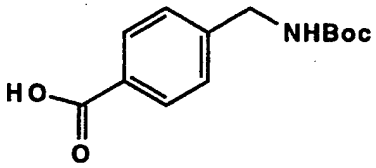


The intermediate from the previous step was stirred in ethyl acetate / HCl for two hours. Prep TLC purification gave 41 mg of the title compound. FAB-MS 592 (M+1).

EXAMPLE 2

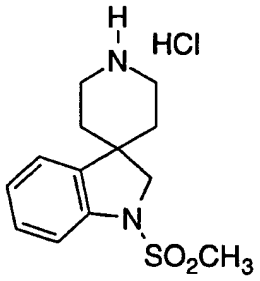


Step A:



To a solution of 1.0g of 4-aminomethylbenzoic acid in 10mL of 1N NaOH, 10mL of water and 20mL of dioxane at 0^0C was 1.7g of ditert-butylcarbonate and stirred overnight. The reaction mixture was acidified to pH=2 and extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous sodium sulfate and concentrated to give the desired compound as a white solid.

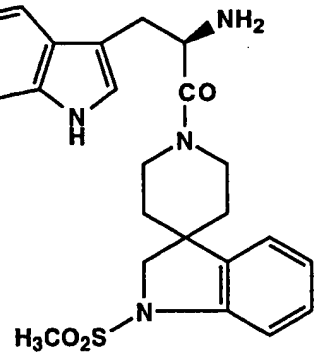
Step B:



To a solution of 1.20 g (5.8mmol) of 1'-methyl-1,2-dihydro-spiro[3H-indole-3,4'-piperdine] (prepared as described in H. Ong et al *J. Med. Chem.* 1983, *23*, 981-986) in 20 mL of dry dichloromethane at 0°C was added triethylamine (0.90 mL; 6.4 mmol) and methanesulfonyl chloride (0.49 mL; 6.35 mmol) and stirred for 30 min. The reaction mixture was poured into 15 mL of saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (2X10 mL). The combined organics were washed with brine (20 mL), dried over anhydrous potassium carbonate, filtered and the solvent removed under reduced pressure to yield 1.44 g of the methanesulfonamide derivative as pale yellow oil which was used without purification.

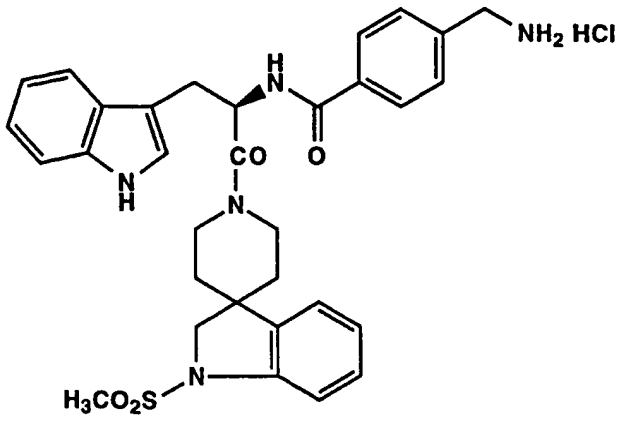
To a solution of above crude product in 20 mL of dry 1,2-dichloroethane at 0°C was added 1.0 mL (9.30 mmol) of 1-chloroethyl chloroformate, and then stirred at RT for 30 min and finally at reflux for 1h. The reaction mixture was concentrated to approximately one third of the volume and then diluted with 20 mL of dry methanol and refluxed for 1.5h. The reaction was cooled to RT and concentrated to approximately one half of the volume. The precipitate was filtered and washed with a small volume of cold methanol. This yielded 1.0 g of the piperidine HCl salt as a white solid. The filtrate was concentrated and a small volume of methanol was added followed by ether. The precipitated material was once again filtered, washed with cold methanol, and dried. This gave an additional 0.49 g of the desired product. Total yield 1.49 g (70%). ^{1}H NMR($CDCl_3$, 200MHz) d 7.43-7.20 (m, 3H), 7.10 (dd, 1H), 3.98 (bs, 2H), 3.55-3.40 (bd, 2H), 3.35-3.10 (m, 2H), 2.99 (s, 3H), 2.15 (t, 2H), 2.00 (t, 2H).

Step C:



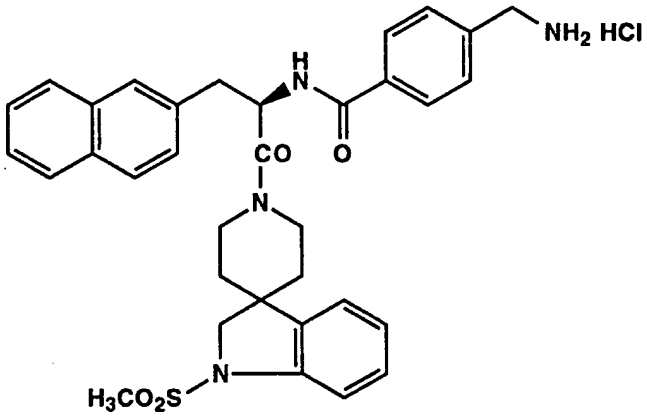
To a suspension of 1.2 g of the piperidine prepared in Step B in 15 mL of acetonitrile was added 0.50 mL of N-methylmorpholine, 1.00 g of (2R, 3R)-N-tBOC-tryptophan, 0.80 g of HOBT, and 1.00 g of EDC and stirred at RT for 3h. The reaction mixture was diluted with 100 mL of ether and washed with 50 mL of 0.05N HCl, 50 mL of saturated sodium bicarbonate solution, dried over $MgSO_4$, and concentrated. A solution of the above intermediate in 50 mL of ethyl acetate at 0°C was treated with HCl (g) for 2 min. and then stirred for 1h. Dry ether (50 mL) was added, and the precipitated solid was collected by filtration.

Step D:



To a solution of 200mg of the amino intermediate from Step C in 5mL of chloroform was added 100mg of the acid intermediate from Step A, 65mg of EDC and 110mg of HOBT and stirred at room temperature for 16h. The reaction mixture was diluted with 20mL of dichloromethane, washed with 0.5N HCl (2X10mL), saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated. This material was purified by flash chromatography with hexane-ethyl acetate (2:1) as the eluent to give the desired product. This material was dissolved in 3mL of ethyl acetate was treated with Hcl (gas) for 1 min. and stirred for 30 minutes. Ether was added and the precipitate was collected by filtration. FABMS Cacld. for C32H33N5O4S 585; Found 586.1 (m+1).

EXAMPLE 3

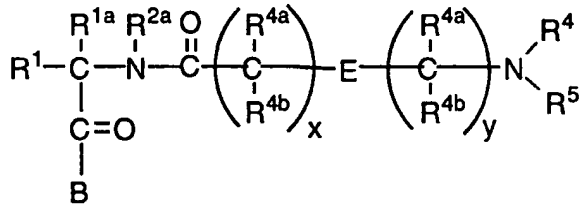


The title compound was prepared from N-tBoc-2-naphthyl alanine and the protected acid synthesized in Step A of Example 2 as described in the experimental for Example 2. FABMS Cacld. for C34H36N4O4S 596; Found 597.2 (m+1).

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula:



Formula I

wherein:

R^1 is selected from the group consisting of:

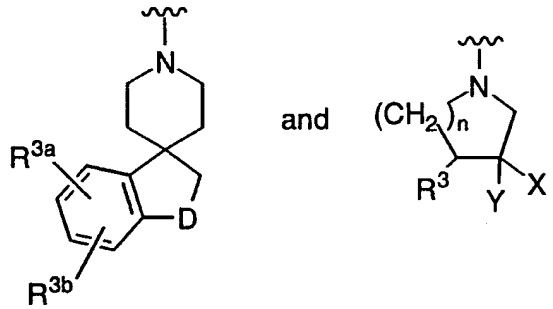
C_1-C_{10} alkyl, -aryl-, aryl (C_1-C_6 alkyl)-, heteroaryl-, heteroaryl(C_1-C_6 alkyl)-, (C_3-C_7 cycloalkyl)-(C_1-C_6 alkyl)-, (C_1-C_5 alkyl)-K-(C_1-C_5 alkyl)-, aryl-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, heteroaryl-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, and (C_3-C_7 cycloalkyl)-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, wherein K is -O-, -$S(O)_m$-, -$N(R^2)C(O)$-, -$C(O)N(R^2)$-,-OC(O)-, -C(O)O-, -CR^2=CR^2- or -C≡C-, wherein R^2 and the alkyl groups may be further substituted with 1 to 9 halo, -$S(O)_mR^{2a}$, 1 to 3 of -OR^{2a}, or -$C(O)OR^{2a}$, and wherein aryl is phenyl or naphthyl, and heteroaryl is selected from indolyl, thiophenyl, benzofuranyl, benzothiopheneyl, aza-indolyl, pyridinyl, quinolinyl, and benzimidazolyl, wherein aryl and heteroaryl are unsubstituted or substituted with phenyl, phenoxy, halophenyl, 1 to 3 of -C_1-C_6 alkyl, 1 to 3 of halo, 1 to 2 of -OR^2, methylenedioxy, -$S(O)_mR^2$, 1 to 2 of -CF_3, -OCF_3, nitro, -$N(R^2)(R^2)$, -$N(R^2)C(O)(R^2)$, -$C(O)OR^2$, -$C(O)N(R^2)(R^2)$, -$SO_2N(R^2)(R^2)$, -$N(R^2)SO_2$-aryl, or -$N(R^2)SO_2R^2$;

R^{1a} is hydrogen or C_1-C_4 alkyl;

R^2 is selected from the group consisting of:
hydrogen, -C_1-C_6 alkyl, -C_3-C_7 cycloalkyl, and -CH_2-phenyl,
wherein the alkyl or the cyloalkyl is unsubstituted or substituted with hydroxyl, C_1-C_3 alkoxy, thioalkyl, $C(O)OR^{2a}$, and where, if two -C_1-C_6 alkyl groups are present on one atom, they may be joined to form a C_3-C_8 cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, optionally substituted by hydroxyl;

R^{2a} is hydrogen or C_1-C_6 alkyl;

B is selected from:

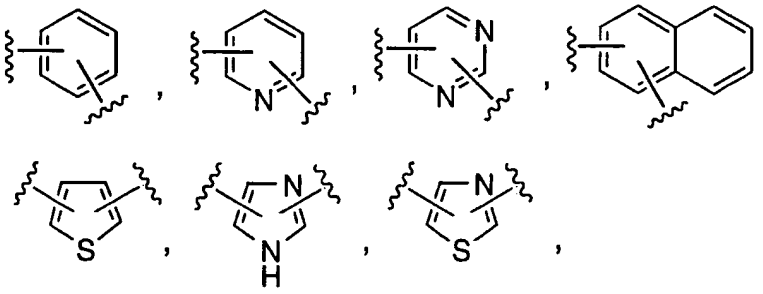


R^3 is selected from: hydrogen, -$(CH_2)_r$phenyl, -$(CH_2)_r$pyridyl, -$(CH_2)_r$thienyl, -$(CH_2)_r$benzimidazolyl, -$(CH_2)_r$quinolinyl, -$(CH_2)_r$naphthyl, -$(CH_2)_r$indolyl, -C_1-C_{10} alkyl, -C_3-C_7 cycloalkyl, where the phenyl, pyridyl, naphthyl, indolyl, thienyl, benzimidazolyl, quinolinyl, and C_3-C_7 cycloalkyl rings may be substituted by 1 to 3 substituents selected from the group consisting of: C_1-C_6 alkyl, halogen, $-OR^2$, $-NHSO_2CF_3$, $-(CH_2)_rOR^6$, $-(CH_2)_rN(R^2)(R^6)$, $-(CH_2)_r(R^6)$, $-(CH_2)_rC(O)OR^2$, $-(CH_2)_rC(O)OR^6$, $-(CH_2)_rOC(O)R^2$, $-(CH_2)_rOC(O)R^6$, $-(CH_2)_rC(O)R^2$, $-(CH_2)_rC(O)R^6$, $-(CH_2)_rC(O)N(R^2)(R^2)$, $-(CH_2)_rC(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)C(O)(R^2)$, $-(CH_2)_rN(R^2)C(O)R^6$ $-(CH^2)_rN(R^6)C(O)R^2$, $-(CH_2)_rN(R^6)C(O)R^6$, $-(CH_2)_rN(R^2)C(O)OR^2$, $-(CH_2)_rN(R^2)C(O)OR^6$, $-(CH_2)_rN(R^6)C(O)OR^2$, $-(CH_2)_rN(R^6)C(O)OR^6$, -

$(CH_2)_rN(R^2)C(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)C(O)N(R^2)(R^2)$, $-(CH_2)_rN(R^6)C(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)SO_2R^2$, $-(CH_2)rN(R^6)SO_2R^2$, $-(CH_2)_rN(R^6)SO_2R^6$, $-(CH_2)_rOC(O)N(R^2)(R^6)$, $-(CH_2)_rOC(O)N(R^2)(R^2)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rOC(O)N(R^2)(R^2)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^2)$, $-(CH_2)_rN(R^2)SO_2N(R^2)(R^6)$, $-(CH_2)_rN(R^6)SO_2N(R^2)(R^6)$, $-(CH_2)_rS(O)_mR^6$, and $-(CH_2)_rS(O)_mR^2$;

R^{3a} and R^{3b} are independently selected from: hydrogen, phenyl, phenoxy, halophenyl, $-C_1$-C_6 alkyl, halogen, $-OR^2$, methylenedioxy, $-S(O)_mR^2$, $-CF_3$, $-OCF_3$, nitro, $-N(R^2)(R^2)$, $-N(R^2)C(O)(R^2)$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, $-N(R^2)SO_2$-aryl, and $-N(R^2)SO^2R^2$;

E is selected from: -O-, -S-, -CH=CH-,



which is optionally substituted with a substituent selected from: halo, hydroxy, $-N(R^2)(R^2)$, C_1-C_6 alkyl and C_1-C_6 alkoxy;

R^4 and R^5 are independently selected from hydrogen, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl where the substituents are selected from halo, hydroxy, phenyl, and C_1-C_6 alkoxycarbonyl;
or R^5 and R^4 may be taken together to form $-(CH_2)_d$-$L_a(CH_2)_e$- where L_a is $-C(R^2)_2$-, -O-, $-S(O)_m$- or $-N(R^2)$-, d and e are independently 1 to 3 and R^2 is as defined above;

R^{4a} and R^{4b} are independently selected from: hydrogen, C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^2$, $-S(O)_mR^2$, $-C(O)OR^2$, C_3-C_7 cycloalkyl, $-N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$; or R^{4a} and R^{4b} may independently be joined to one or both of R^4 or E (where E is other than -O-, -S-, or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^{4a} or R^{4b} and the R^4 E group, wherein the bridge contain 1 to 8 carbons atoms; or R^{4a} and R^{4b} may be joined to one another to form C_3-C_7 cycloalkyl;

R^6 is selected from: hydrogen, C_1-C_6 alkyl, and $(CH_2)_v$aryl, wherein the $(CH_2)_v$ and alkyl groups may be optionally substituted by $-O(R^2)$, $-S(O)_mR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, or $-N(R^2)C(O)N(R^2)(R^2)$, wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C_1-C_6 alkyl, C_3-C_6 cycloalkyl, amino, or hydroxyl;

X is selected from the group consisting of: hydrogen, $-C\equiv N$, $-(CH_2)_qN(R^2)C(O)R^2$, $-(CH_2)_qN(R^2)C(O)(CH_2)_t$aryl, $-(CH_2)_qN(R^2)SO_2(CH_2)_t$aryl, $-(CH_2)_qN(R^2)SO_2R^2$, $-(CH_2)_qN(R^2)C(O)N(R^2)(CH_2)_t$aryl, $-(CH_2)_qN(R^2)C(O)N(R^2)(R^2)$, $-(CH_2)_qC(O)N(R^2)(R^2)$, $-(CH_2)_qC(O)N(R^2)(CH_2)_t$aryl, $-(CH_2)_qC(O)OR^2$, $-(CH_2)_qC(O)O(CH_2)_t$aryl, $-(CH_2)_qOR^2$, $-(CH2)_qOC(O)R^2$, $-(CH_2)_qOC(O)(CH^2)_t$aryl, $-(CH_2)_qOC(O)N(R^2)(R^2)$, $-(CH_2)_qC(O)R^2$, $-(CH_2)_qC(O)(CH_2)_t$aryl, $-(CH_2)_qN(R^2)C(O)OR^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)(R^2)$, $-(CH_2)_qS(O)_mR^2$, and $-(CH_2)_qS(O)_m(CH_2)_t$aryl, where R^2, $(CH_2)_q$ and $(CH_2)_t$ group may be optionally substituted with C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $N(R^2)(R^2)$, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted with

halogen, -OR^2, -$CON(R^2)(R^2)$, -$C(O)OR^2$, C_1-C_4 alkyl, -$S(O)_mR^2$, or 1H-tetrazol-5-yl;

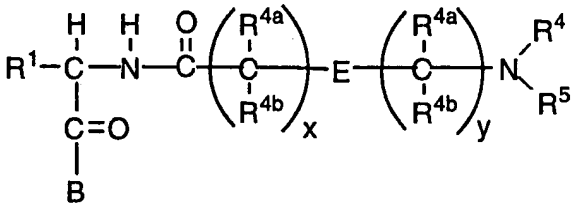
Y is selected from the group consisting of:
hydrogen, C_1-C_{10} alkyl, -$(CH_2)_t$aryl, -$(CH_2)_q$(C_3-C_7 cycloalkyl), -$(CH_2)_q$-K-(C_1-C_6 alkyl), -$(CH_2)_q$-K-$(CH_2)_t$aryl, -$(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl containing O, NR^2 S) and -$(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl), where K is -O-, -$S(O)_m$-, -$C(O)NR^2$-, -CH=CH-, -C≡C-, -$N(R^2)C(O)$-, -$C(O)NR^2$-, -C(O)O-, or -OC(O)-, and where the alkyl, R^2, $(CH_2)q$ and $(CH_2)_t$ groups are optionally substituted by C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, -$CONH_2$ or a carboxylate C_1-C_4 alkyl ester, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazoly, indolyl, oxadiazoyl, pyrimidinyl, thiadiazolyl,pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrrazinyl, or isothiazolyl which is optionally substituted with halogen, -OR^2, -$C(O)OR^2$, $N(R^2)(R^2)$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, C_1-C_4 alkyl, -$S(O)_mR^2$, or 1H-tetrazol-5-yl;

D is selected from: -$N(R^7)$-, -$S(O)_m$-, -C(O)- and -$C(H)(R^7)$-, wherein R^7 is selected from: -R^2, -OR^2, -$(CH_2)_q$aryl, -$C(O)R^2$, -$C(O)(CH_2)_q$aryl, -SO_2R^2, -$SO_2(CH_2)_q$aryl, -$C(O)N(R^2)(R^2)$, -$C(O)N(R^2)(CH_2)_q$aryl, -$C(O)OR^2$, 1-H-tetrazol-5-yl, -$SO_2N(R^2)$aryl, -$SO_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C_1-C_4 alkyl, and the R^2 and aryl may be optionally further substituted with a substituent selected from: -OR^{2a}, -$O(CH_2)_q$ aryl, -$C(O)OR^{2a}$, -$C(O)(CH_2)_q$ aryl, -$C(O)N(R^{2a})(R^{2a})$, -$C(O)N(R^{2a})(CH_2)1$ aryl, halogen, -$N(R^{2a})(R^{2a})$, -C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, -$C(O)NHSO_2R^{2a}$, -$S(O)_mR^{2a}$, -$C(O)NHSO_2(CH_2)_q$aryl, -$N(R^2)C(O)N(R^{2a})(R^{2a})$, -$N(R^{2a})C(O)N(R^{2a})(CH_2)_q$aryl, -$N(R^{2a})(R^{2a})$, -$N(R^{2a})C(O)R^{2a}$), -$N(R^{2a})C(O)(CH_2)_q$ aryl, -$OC(O)N(R^{2a})(R^{2a})$, -$OC(O)N(R^{2a})(CH_2)_q$ aryl;

l is 0, 1 or 2;
m is 0, 1, or 2;
n is 0, 1, or 2;
q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2;
x is 0, 1, 2, or 3;
y is 0, 1, 2, or 3, with the proviso that if E is -O- or -S-, y is other than 0 or 1, and with the further proviso that if E is -CH=CH-, y is other than 0;

and pharmaceutically acceptable salts and individual diastereomers thereof.

2. The compound of Claim 1 of the formula:



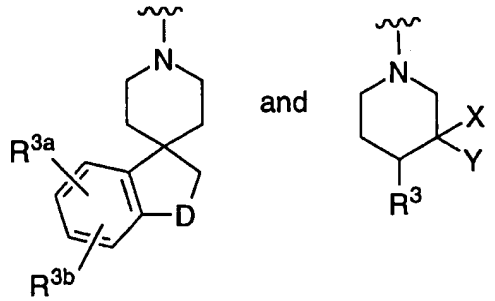
Formula Ia

wherein:
R^1 is selected from the group consisting of:
C_1-C_{10} alkyl, -aryl-, aryl (C_1-C_6 alkyl)-,
heteroaryl-, heteroaryl(C_1-C_6 alkyl)-,
(C_3-C_7 cycloalkyl)-(C_1-C_6 alkyl)-,
(C_1-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
aryl-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
heteroaryl-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-, and
(C_3-C_7 cycloalkyl)-(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl)-,
wherein K is -O-, -S(O)$_m$-, -N(R^2)C(O)-, -C(O)N(R^2)-,-OC(O)-,
-C(O)O-, -CR^2=CR^2- or -C≡C-,

wherein R^2 and the alkyl groups may be further substituted with 1 to 9 halo, $-S(O)_mR^{2a}$, 1 to 3 of $-OR^{2a}$, or $-C(O)OR^{2a}$, and wherein aryl is phenyl or naphthyl, and heteroaryl is selected from indolyl, thiophenyl, benzofuranyl, benzothiopheneyl, aza-indolyl, pyrindinyl, quinolinyl, and benzimidazolyl, wherein aryl and heteroaryl are unsubstituted or substituted with phenyl, phenoxy, halophenyl, 1 to 3 of $-C_1$-C_6 alkyl, 1 to 3 of halo, 1 to 2 of $-OR^2$, methylenedioxy, $-S(O)_mR^2$, 1 to 2 of $-CF_3$, $-OCF_3$, nitro, $-N(R^2)(R^2)$, $-N(R^2)C(O)(R^2)$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, $-N(R^2)SO_2$-aryl, or $-N(R^2)SO_2R^2$;

R^2 is selected from the group consisting of:
hydrogen, $-C_1$-C_6 alkyl, $-C_3$-C_7 cycloalkyl, and $-CH_2$-phenyl, wherein the alkyl or the cyloalkyl is unsubstituted or substituted with hydroxyl, C_1-C_3 alkoxy, thioalkyl, $-C(O)OR^{2a}$, and wherein, if two $-C_1$-C_6 alkyl groups are present on one atom, the groups may be optionally joined to form a C_3-C_8 cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine;

B is selected from:

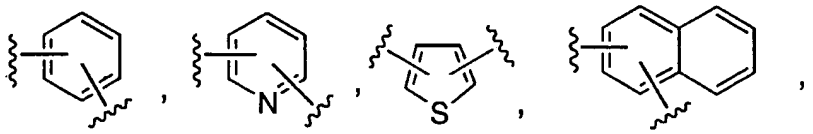


R^3 is selected from: hydrogen, phenyl, pyridyl, naphthyl, indolyl, benzimidazolyl, thienyl, quinolinyl, where the phenyl, pyridyl, naphthyl, benzimidazolyl, thienyl, quinolinyl, and indolyl may be substituted by 1 to 3 substituents selected from the group consisting of: C_1-C_6 alkyl, halogen, $-OR^2$, $-(CH_2)_rOR^6$, $-(CH_2)_rN(R^2)(R^6)$, $-(CH_2)_r(R^6)$, -

$(CH_2)_rC(O)OR^2$, $-(CH_2)_rC(O)OR^6$, $-(CH_2)_rC(O)R^2$, $-(CH_2)_rC(O)R^6$, $-(CH_2)_rC(O)N(R^2)(R^2)$, $-(CH_2)_rC(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)C(O)(R^2)$, $-(CH_2)_rN(R^2)C(O)R^6$ $-(CH_2)_rN(R^6)C(O)R^2$, $-(CH_2)_rN(R^6)C(O)R^6$, $-(CH_2)_rN(R^2)C(O)OR^2$, $-(CH_2)_rN(R^2)C(O)OR^6$, $-(CH_2)_rN(R^6)C(O)OR^2$, $-(CH_2)_rN(R^6)C(O)OR^6$, $-(CH_2)_rN(R^2)C(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)C(O)N(R^2)(R^2)$, $-(CH_2)_rN(R^6)C(O)N(R^2)(R^6)$, $-(CH_2)_rN(R^2)SO_2R^2$, $-(CH_2)rN(R^6)SO_2R^2$, $-(CH_2)_rN(R^6)SO_2R^6$, $-(CH_2)_rOC(O)N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^2)$, $-(CH_2)_rS(O)_mR^6$, and $-(CH_2)_rS(O)_mR^2$;

R^{3a} and R^{3b} are independently selected from: hydrogen, phenyl, phenoxy, halophenyl, $-C_1$-C_6 alkyl, halogen, $-OR^2$, methylenedioxy, $-S(O)_mR^2$, $-CF_3$, $-OCF_3$, nitro, $-N(R^2)(R^2)$, $-N(R^2)C(O)(R^2)$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, $-N(R^2)SO_2$-aryl, and $-N(R^2)SO^2R^2$;

E is selected from: -O-, -S-, -CH=CH-,



which is optionally substituted with a substituent selected from: halo, hydroxy, $-N(R^2)(R^2)$, C_1-C_6 alkyl and C_1-C_6 alkoxy;

R^4 and R^5 are independently selected from hydrogen, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl where the substituents are selected from halo, hydroxy, phenyl, and C_1-C_6 alkoxycarbonyl;

or R^5 and R^4 may be taken together to form $-(CH_2)_d$-$L_a(CH_2)_e$- where L_a is $-C(R^2)_2$-, -O-, $-S(O)_m$- or $-N(R^2)$-, d and e are independently 1 to 3 and R^2 is as defined above;

R^{4a} and R^{4b} are independently selected from: hydrogen, C_1-C_6 alkyl, trifluoromethyl, phenyl, or substituted C_1-C_6 alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, p-hydroxyphenyl, $-OR^2$, $-S(O)_mR^2$, $-C(O)OR^2$, C_3-C_7 cycloalkyl, $-N(R^2)(R^2)$, $-C(O)N(R^2)(R^2)$; or R^{4a} and R^{4b} may independently be joined to one or both of R^4 or E (were E is other than -O-, -S-, or -CH=CH-) to form an alkylene bridge between the terminal nitrogen and the alkyl portion of the R^{4a} or R^{4b} and the R^4 E group, wherein the bridge contain 1 to 5 carbons atoms; or R^{4a} and R^{4b} may be joined to one another to form C_3-C_7 cycloalkyl;

R^6 is selected from: hydrogen, C_1-C_6 alkyl, and $(CH_2)_v$aryl, wherein the $(CH_2)_v$ and alkyl groups may be optionally substituted by $-O(R^2)$, $-S(O)_mR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, or $-N(R^2)C(O)N(R^2)(R^2)$, wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C_1-C_6 alkyl, C_3-C_6 cycloalkyl, amino, or hydroxyl;

X is selected from the group consisting of: hydrogen, $-C\equiv N$, $-(CH_2)_qN(R^2)C(O)R^2$, $-(CH_2)_qN(R^2)C(O)(CH_2)_t$aryl, $-(CH_2)_qN(R^2)SO_2(CH_2)_t$aryl, $-(CH_2)_qN(R^2)SO_2R^2$, $-(CH_2)_qN(R^2)C(O)N(R^2)(CH_2)_t$aryl, $-(CH_2)_qN(R^2)C(O)N(R^2)(R^2)$, $-(CH_2)_qC(O)N(R^2)(R^2)$, $-(CH_2)_qC(O)N(R^2)(CH_2)_t$aryl, $-(CH_2)_qC(O)OR^2$, $-(CH_2)_qC(O)O(CH_2)_t$aryl, $-(CH_2)_qOR^2$, $-(CH2)_qOC(O)R^2$, $-(CH_2)_qOC(O)(CH^2)_t$aryl, $-(CH_2)_qOC(O)N(R^2)(R^2)$, $-(CH_2)_qC(O)R^2$, $-(CH_2)_qC(O)(CH_2)_t$aryl, $-(CH_2)_qN(R^2)C(O)OR^2$, $-(CH_2)_qN(R^2)SO_2N(R^2)(R^2)$, $-(CH_2)_qS(O)_mR^2$, and $-(CH_2)_qS(O)_m(CH_2)_t$aryl, where R^2, $(CH_2)_q$ and $(CH_2)_t$ group may be optionally substituted with C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, $N(R^2)(R^2)$, $CONH_2$, $S(O)_mCH_3$, carboxylate C_1-C_4 alkyl esters, or 1H-tetrazol-5-yl, and aryl is phenyl, naphthyl, pyridyl, thiazolyl, or 1H-tetrazol-5-yl groups which may be optionally substituted with

halogen, -OR^2, -$CON(R^2)(R^2)$, -$C(O)OR^2$, C_1-C_4 alkyl, -$S(O)_mR^2$, or 1H-tetrazol-5-yl;

Y is selected from the group consisting of:
hydrogen, C_1-C_{10} alkyl, -$(CH_2)_t$aryl, -$(CH_2)_q$(C_3-C_7 cycloalkyl), -$(CH_2)_q$-K-(C_1-C_6 alkyl), -$(CH_2)_q$-K-$(CH_2)_t$aryl, -$(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl containing O, NR^2 S) and -$(CH_2)_q$-K-$(CH_2)_t$(C_3-C_7 cycloalkyl), where K is O, $S(O)_m$, $C(O)NR^2$, CH=CH, C≡C, $N(R^2)C(O)$, $C(O)NR^2$, C(O)O, or OC(O), and where the alkyl, R^2, $(CH_2)_q$ and $(CH_2)_t$ groups are optionally substituted by C_1-C_4 alkyl, hydroxyl, C_1-C_4 lower alkoxy, carboxyl, -$CONH_2$ or a carboxylate C_1-C_4 alkyl ester, and aryl is phenyl, naphthyl, pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazoly, indolyl, oxadiazoyl, pyrimidinyl, thiadiazolyl,pyrazolyl, oxazolyl, isoxazolyl, thiopheneyl, quinolinyl, pyrrazinyl, or isothiazolyl which is optionally substituted with halogen, -OR^2, -$C(O)OR^2$, $N(R^2)(R^2)$, -$C(O)N(R^2)(R^2)$, nitro, cyano, benzyl, C_1-C_4 alkyl, -$S(O)_mR^2$, or 1H-tetrazol-5-yl;

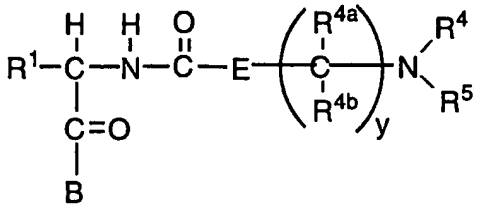
D is selected from: -$N(R^7)$-, -$S(O)_m$-, -C(O)- and -$C(H)(R^7)$-, wherein R^7 is selected from: -R^2, -$(CH_2)_q$aryl, -$C(O)R^2$, -SO_2R^2, -$C(O)N(R^2)(R^2)$, -$C(O)OR^2$, 1-H-tetrazol-5-yl, -$SO_2N(R^2)$aryl, -$SO_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C_1-C_4 alkyl, and the R^2 and aryl may be optionally further substituted with a substituent selected from: -OR^{2a}, -$C(O)OR^{2a}$, -$C(O)N(R^{2a})(R^{2a})$, halogen, -C_1-C_4 alkyl, and the aryl is selected from of triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, and 1H-tetrazolyl;

l is 0, 1 or 2;
m is 0, 1, or 2;
q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2;

x is 0, 1, 2, or 3;
y is 0, 1, 2, or 3, with the proviso that if E is -O- or -S-, y is other than 0 or 1, and with the further proviso that if E is -CH=CH-, y is other than 0;

and pharmaceutically acceptable salts and individual diastereomers thereof.

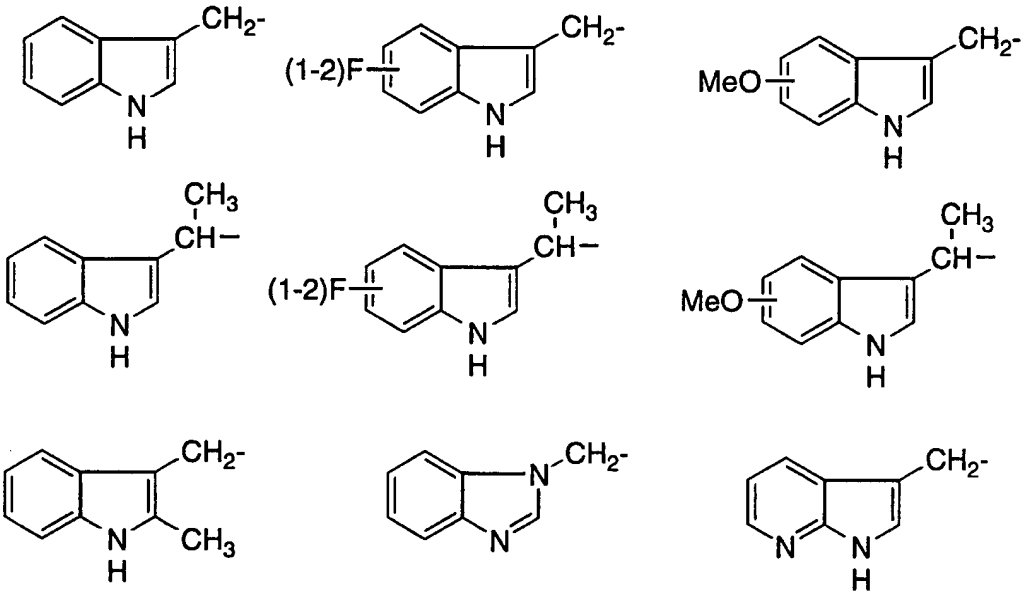
3. The compound of Claim 1 of the formula:

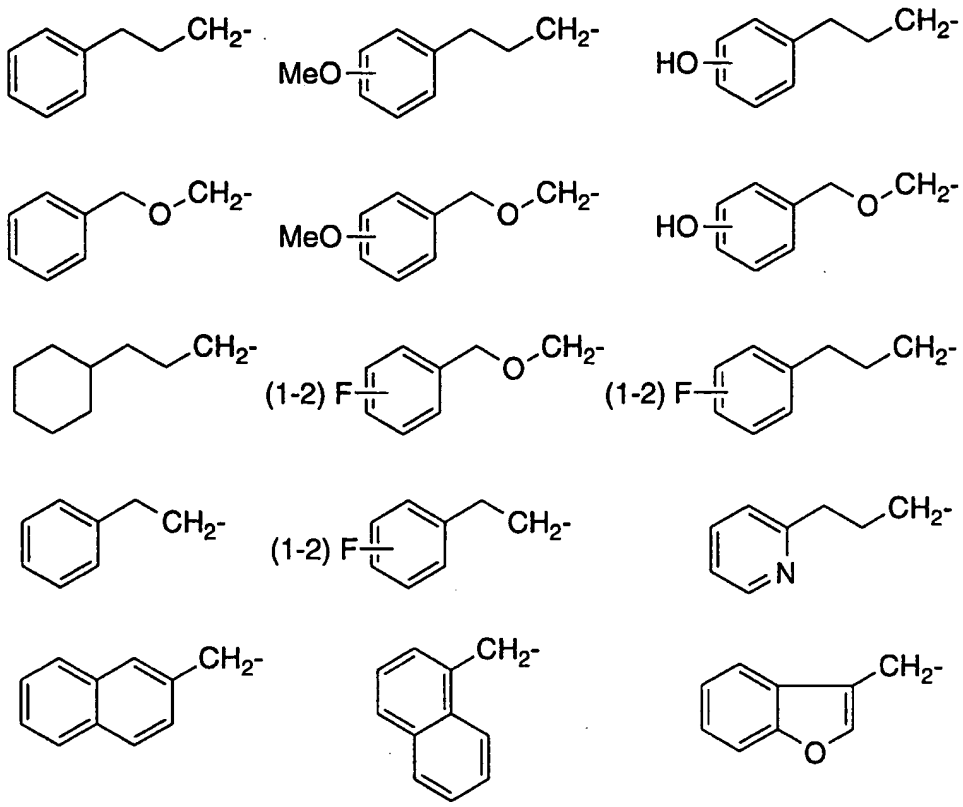


Formula Ib

wherein:

R^1 is selected from the group consisting of:



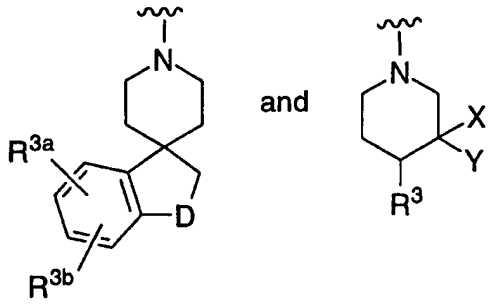


or their regioisomers where not specified;

R^2 is selected from the group consisting of:
hydrogen, -C_1-C_6 alkyl, -C_3-C_7 cycloalkyl, and -CH_2-phenyl, wherein the alkyl or the cyloalkyl is unsubstituted or substituted with hydroxyl, C_1-C_3 alkoxy, thioalkyl, -C(O)OR^{2a}, and wherein, if two -C_1-C_6 alkyl groups are present on one atom, the groups may be optionally joined to form a C_3-C_8 cyclic ring being selected from the group consisting of pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine;

R^{2a} is hydrogen, or C_1-C_4 alkyl;

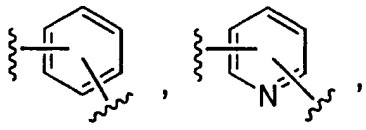
B is selected from:



R^3 is selected from: hydrogen or phenyl, wherein the phenyl is substituted in the ortho position by a substituent selected from the group consisting of: C_1-C_6 alkyl, halogen, $-OR^2$, $-(CH_2)_rOR^6$, $-(CH_2)_rN(R^2)(R^6)$, $-(CH_2)_r(R^6)$, $-(CH_2)_rC(O)OR^2$, $-(CH_2)_rC(O)OR^6$, $-(CH_2)_rC(O)R^2$, $-(CH_2)_rC(O)R^6$, $-(CH_2)_rC(O)N(R^2)(R^2)$, $-(CH_2)_rC(O)N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^6)$, $-(CH_2)_rSO_2N(R^2)(R^2)$, $-(CH_2)_rS(O)_mR^6$, and $-(CH_2)_rS(O)_mR^2$;

R^{3a} and R^{3b} are independently selected from: hydrogen, $-C_1$-C_6 alkyl and halogen;

E is selected from: -O-, -CH=CH-,



which is optionally substituted with a substituent selected from: halo, hydroxy, $-N(R^2)(R^2)$, C_1-C_6 alkyl and C_1-C_6 alkoxy;

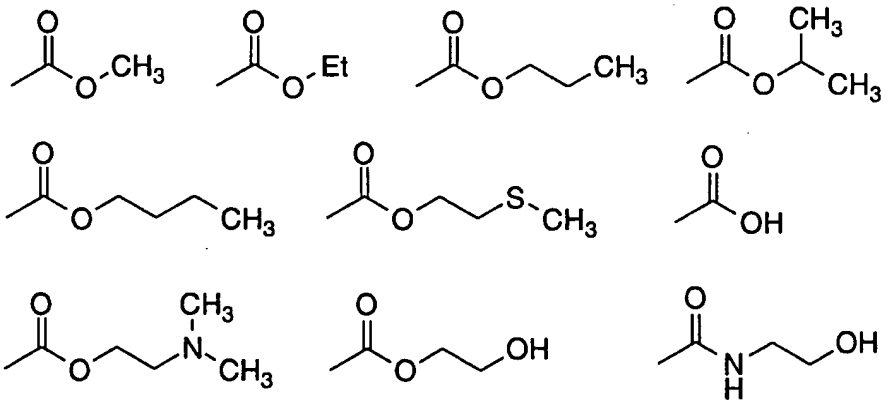
R^4 and R^5 are independently selected from hydrogen, C_1-C_6 alkyl, and substituted C_1-C_6 alkyl where the substituents are selected from halo, hydroxy, phenyl, and C_1-C_6 alkoxycarbonyl;

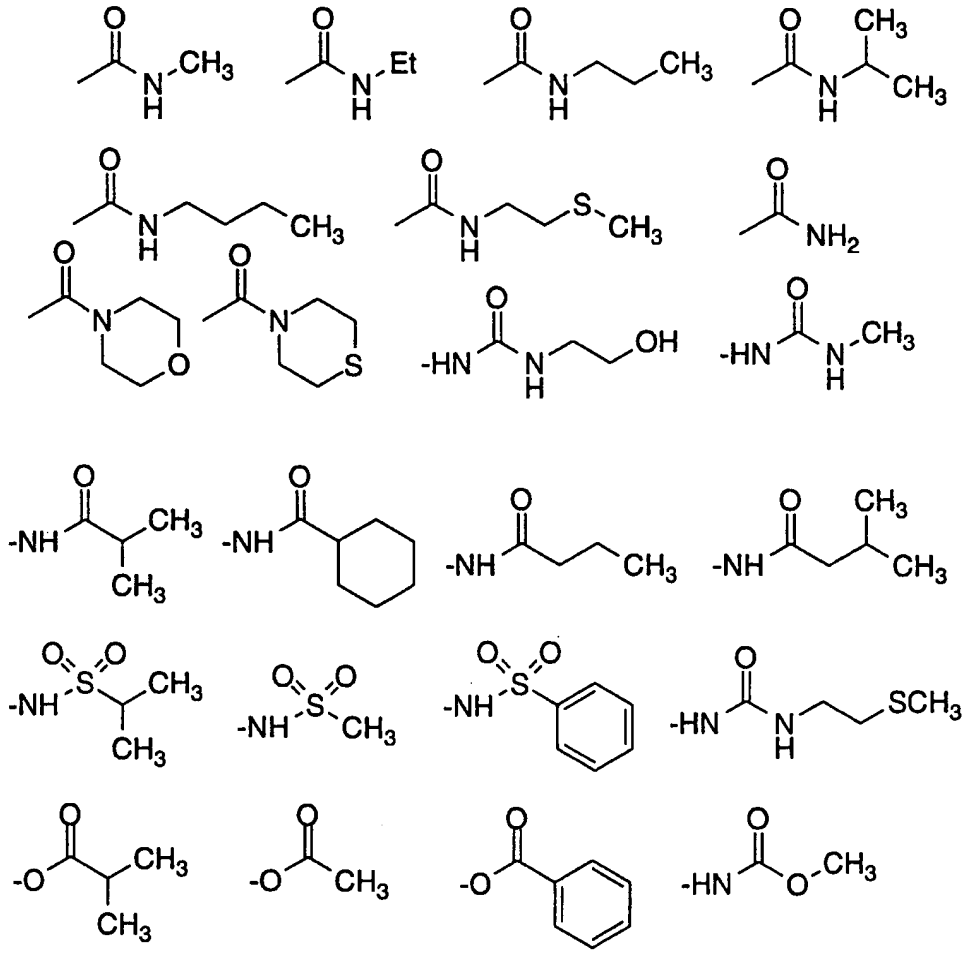
or R^5 and R^4 may be taken together to form $-(CH_2)_d-L_a(CH_2)_e-$ where L_a is $-C(R^2)_2-$, -O-, $-S(O)_m-$ or $-N(R^2)-$, d and e are independently 1 to 3 and R^2 is as defined above;

R^{4a} and R^{4b} are independently selected from: hydrogen, C_1-C_6 alkyl, or substituted C_1-C_6 alkyl where the substituents are selected from: imidazolyl, naphthyl, phenyl, indolyl, and p-hydroxyphenyl;

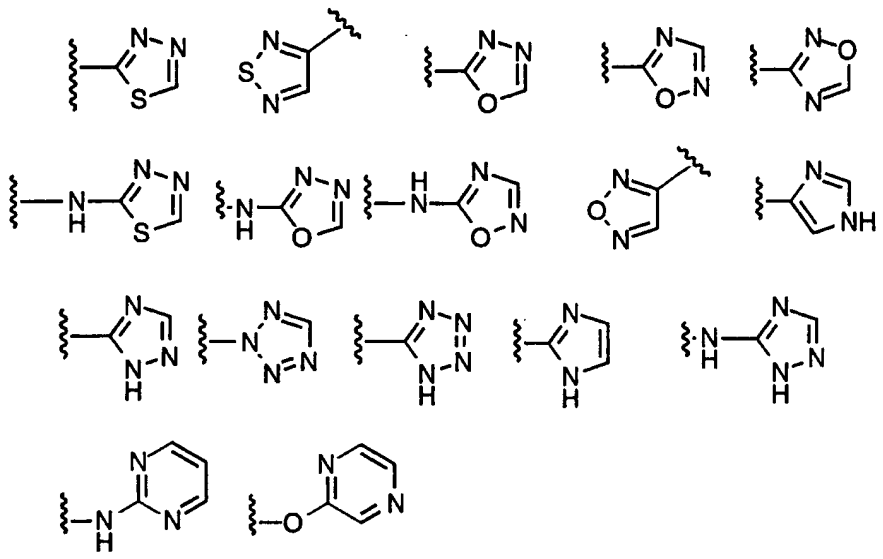
R^6 is selected from: hydrogen, C_1-C_6 alkyl, and $(CH_2)_v$aryl, wherein the $(CH_2)_v$ and alkyl groups may be optionally substituted by $-O(R^2)$, $-S(O)_mR^2$, $-C(O)OR^2$, $-C(O)N(R^2)(R^2)$, $-SO_2N(R^2)(R^2)$, or $-N(R^2)C(O)N(R^2)(R^2)$, wherein the aryl group is selected from: phenyl, pyridyl, 1H-tetrazolyl, triazolyl, oxadiazolyl, pyrazolyl, thiadiazoyl, and benzimidazol-2-yl, which is optionally substituted with C_1-C_6 alkyl, C_3-C_6 cycloalkyl, amino, or hydroxyl;

X is selected from the group consisting of: hydrogen,



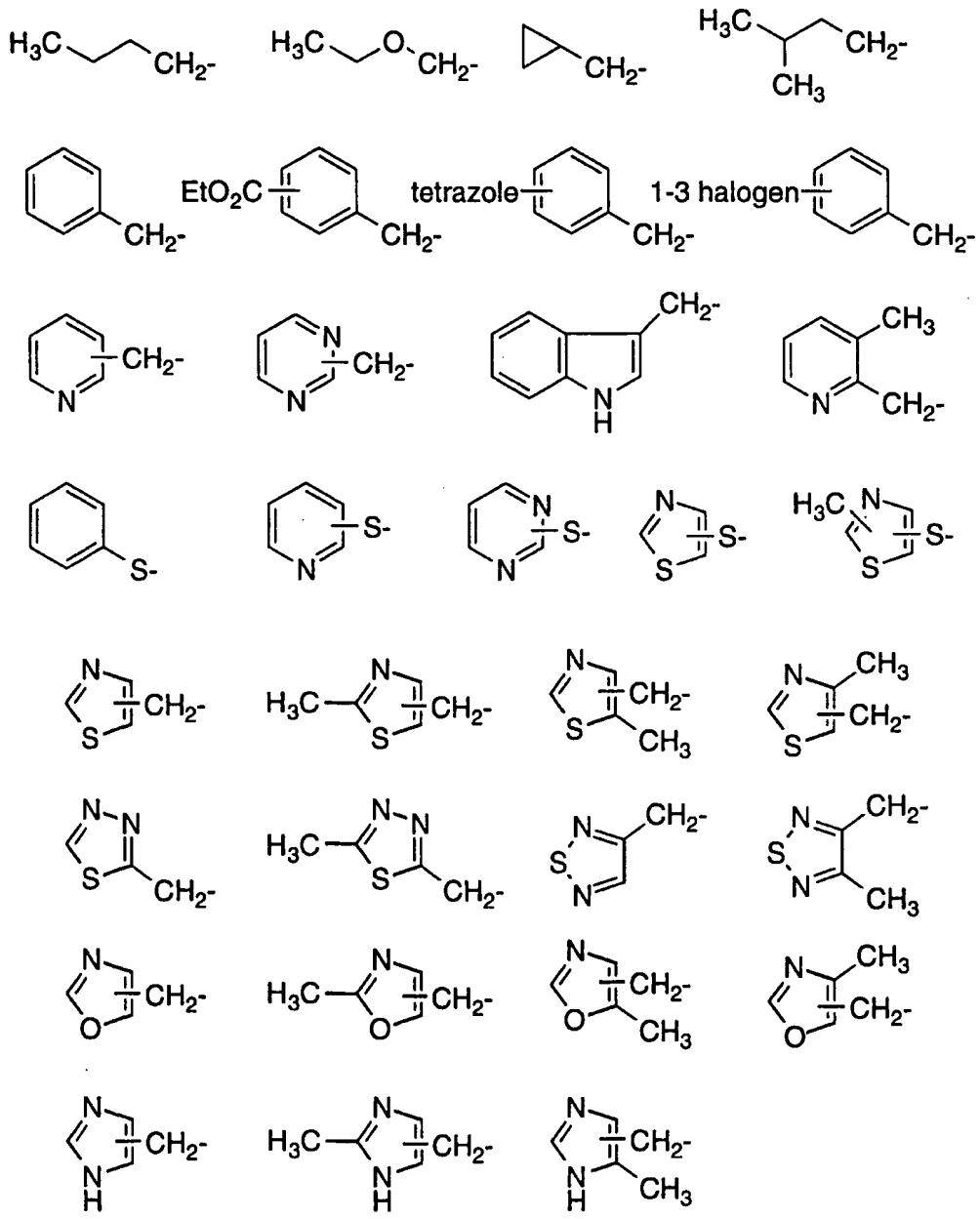


and further selected from the following group of heterocycles



wherein the heterocycle is optionally substituted with a substituent selected from: $-N(R^2)(R^2)$, $-O(R^2)$, C_1-C_3 alkyl, halogen, and trifluoromethyl;

Y is selected from the group consisting of: hydrogen,



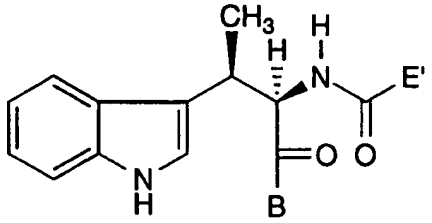
or their regioisomers whereof where not specified;

D is selected from: $-N(R^7)-$, $-S(O)_m-$, -C(O)- and $-C(H)(R^7)-$, wherein R^7 is selected from: $-R^2$, $-(CH_2)_q$aryl, $-C(O)R^2$, $-SO_2R^2$, $-C(O)N(R^2)(R^2)$, $-C(O)OR^2$, 1-H-tetrazol-5-yl, $-SO_2N(R^2)$aryl, $-SO_2N(R^2)(R^2)$ and the $(CH_2)_q$ may be optionally substituted by C_1-C_4 alkyl, and the R^2 and aryl may be optionally further substituted with a substituent selected from: $-OR^{2a}$, $-C(O)OR^{2a}$, $-C(O)N(R^{2a})(R^{2a})$, halogen, $-C_1$-C_4 alkyl, and the aryl is selected from of triazolyl, oxadiazolyl, 1H-tetrazolyl, and thiadiazolyl;

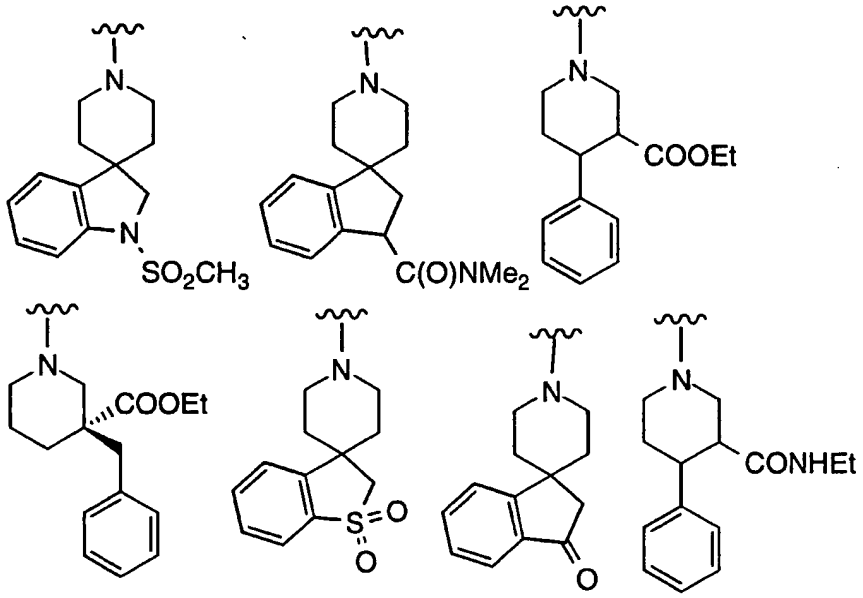
l is 0, 1 or 2;
m is 0, 1, or 2;
q is 0, 1, 2, 3, or 4;
r is 0, 1, 2, or 3;
t is 0, 1, 2, or 3;
v is 0, 1, or 2;
y is 1 or 2, with the proviso that if E is -O-, y is 2;

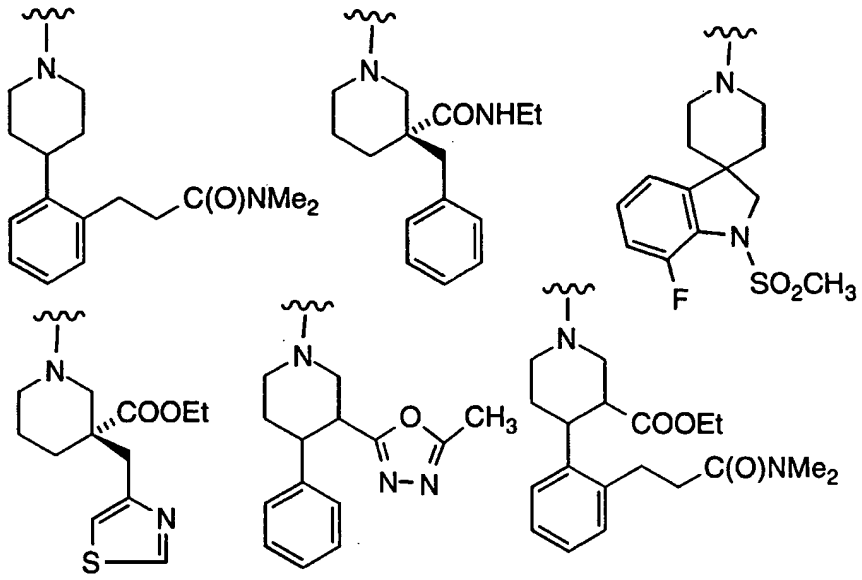
and pharmaceutically acceptable salts and individual diastereomers thereof.

4. The compound of Claim 1 of the formula:



wherein B is selected from the group consisting of:





E' is selected from:

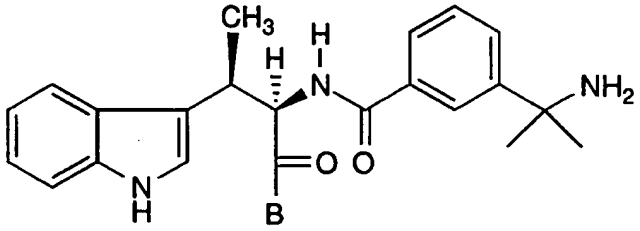
-CH=CH-CH_2-NH_2, -CH=CH-CH(CH_3)-NH_2,

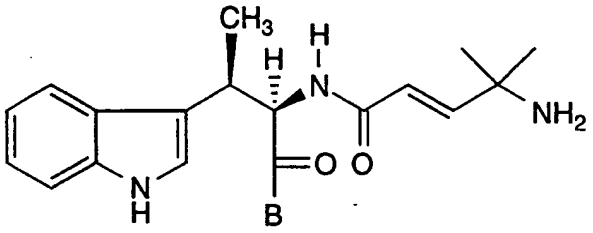
-CH=CH-C(CH_3)2-NH_2,

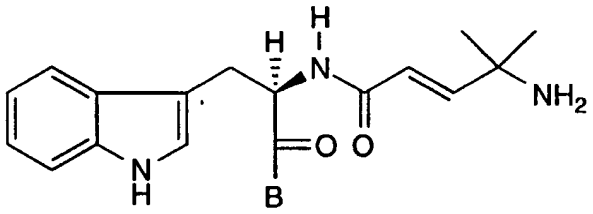
or phenyl substituted with -CH_2-NH_2, -CH(CH_3)-NH_2, or -C(CH_3)2-NH_2;

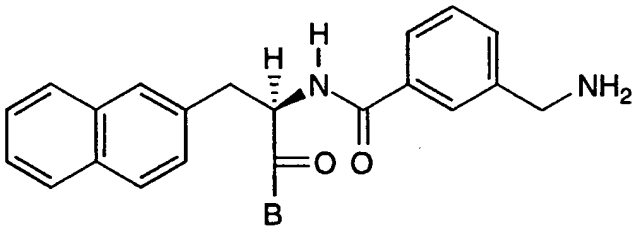
and pharmaceutically acceptable salts and individual diastereomers thereof.

5. The compound of Claim 4 of the formula:

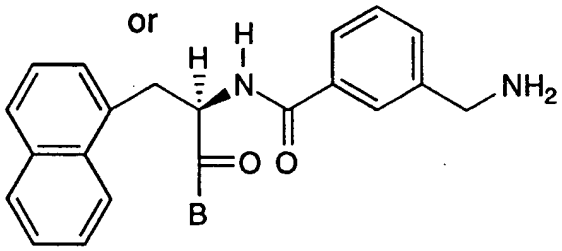




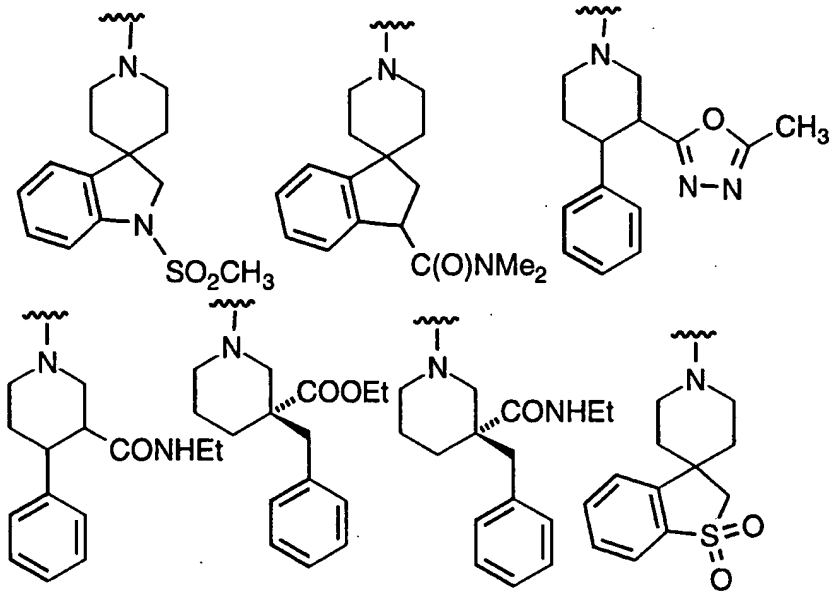




or

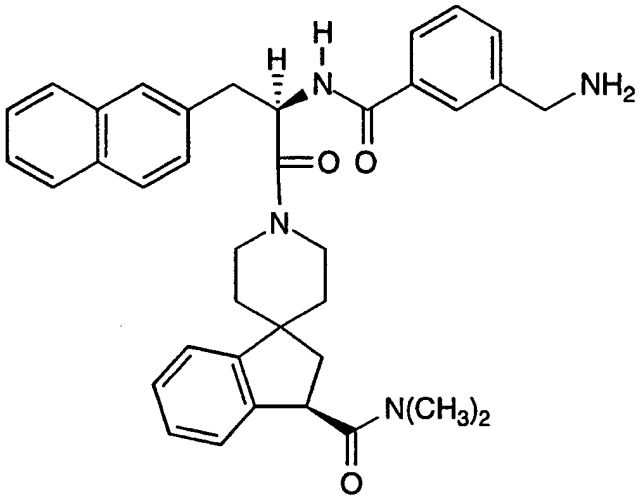


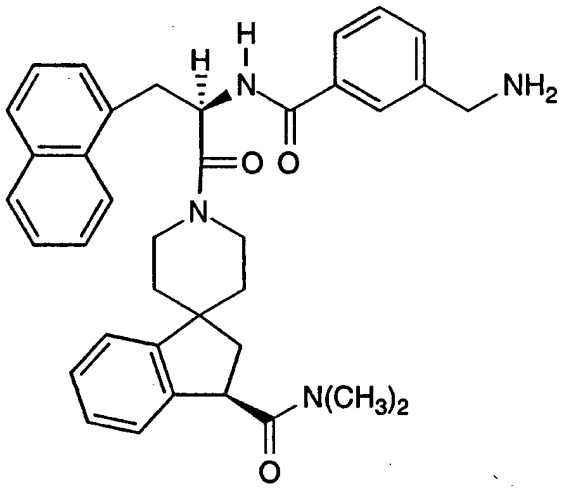
wherein B is selected from the group consisting of:

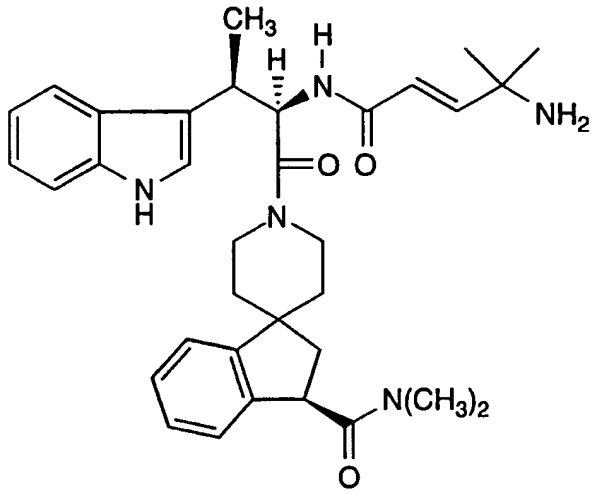


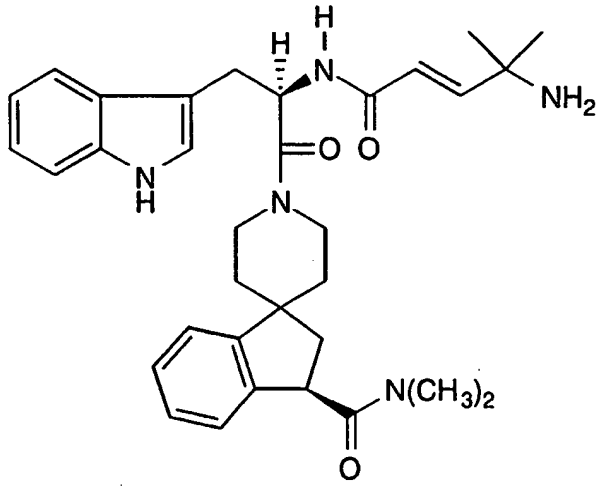
and pharmaceutically acceptable salts and individual diastereomers thereof.

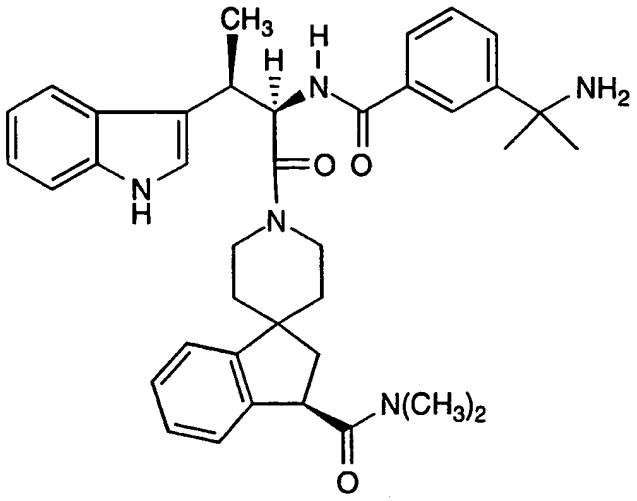
6. A compound which is selected from the group consisting of:






CH3
H
H
N
NH2
O
O
N
H
N
N(CH3)2
O


H
H
N
NH2
O
O
N
H
N
N(CH3)2
O



and pharmaceutically acceptable salts and individual diastereomers thereof where not otherwise specified.

7. A pharmaceutical composition which comprises an inert carrier and the compound of Claim 1.

8. A pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or an animal which comprises an inert carrier and an effective amount of the compound of Claim 1 in combination with an additional growth hormone secretagogue.

9. A pharmaceutical composition useful for the treatment of osteoporosis which comprises a combination of a bisphosphonate compound and the compound of Claim 1.

10. The pharmaceutical composition of Claim 9 wherein the bisphosphonate compound is alendronate.

11. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of the compound of Claim 1.

12. A method for increasing levels of endogenous growth hormone in a human or an animal which comprises administering to such human or animal an effective amount of the compound of Claim 1 in combination with an additional growth hormone secretagogue.

13. The method of Claim 12 wherein the additional growth hormone secretagogue is selected from the group consisting of: growth hormone releasing factor; an analog of growth hormone releasing factor; IGF-1; and IGF-2.

14. A method for increasing feed efficiency, promoting growth, increasing milk production and improving the carcass quality of livestock which comprises administering to such livestock an effective amount of the compound of Claim 1.

15. A method for the treatment of a disease or a condition which is benefited by the anabolic effects of enhanced growth hormone levels that comprises administering to a patient in need thereof an effective amount the compound of Claim 1.

16. The method of Claim 15 wherein the disease or condition is selected from the group consisting of: osteoporosis; catabolic illness; immune deficiency, including that in individuals with a depressed T4/T8 cell ratio; bone fracture; musculoskeletal impairment in the elderly; growth hormone deficiency in adults or in children; short stature in children; obesity; sleep disorders; cachexia and protein loss due to chronic illness such as AIDS or cancer; and the treatment of patients recovering from major surgery, wounds or burns.

17. A method for the treatment of osteoporosis which comprises administering to a patient with osteoporosis a combination of a bisphosphonate compound and the compound of Claim 1.

18. The method of Claim 17 wherein the bisphosphonate compound is alendronate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/16103

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE
search terms: growth(w)hormone, secret?, produc?, piperidin?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,536,716 A (CHEN et al) 16 July 1996, see entire document.	1-18 --- 1-18
X --- Y	US 5,492,920 A (CHEN et al) 20 February 1996, see entire document.	1-18 --- 1-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 04 NOVEMBER 1997	Date of mailing of the international search report 19 NOV 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JANE C. OSWECKI Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/16103

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-18

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/16103

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A01N 43/08, 43/10, 43/26, 43/40, 43/74, 43/90; A61K 31/445; C07D 211/20, 211/26, 401/04, 401/12, 401/14, 405/04, 405/14, 409/14, 413/14, 417/14, 471/10

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/278, 318, 320, 321, 322, 323, 324, 326, 331, 333, 338, 339, 340, 342, 344, 357; 546/18, 193, 194, 196, 197, 198, 199, 201, 202, 205, 208, 209, 210, 211, 212, 213, 214, 215, 227, 228, 229, 230, 232, 237, 245

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/278, 318, 320, 321, 322, 323, 324, 326, 331, 333, 338, 339, 340, 342, 344, 357; 546/18, 193, 194, 196, 197, 198, 199, 201, 202, 205, 208, 209, 210, 211, 212, 213, 214, 215, 227, 228, 229, 230, 232, 237, 245

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claims 1 and 6, drawn to spiro compounds of Formula I and comprising a piperidine-containing spiro moiety as substituent B.

Group II, claims 1 and 6, drawn to non-spiro containing compounds of Formula I and comprising a piperidine moiety as substituent B.

Group III, claims 1 and 6, drawn to non-spiro containing compounds of Formula I and comprising a pyrrolidine moiety as substituent B.

Group IV, claims 1 and 6, drawn to non-spiro containing compounds of Formula I and comprising an azepine moiety as substituent B.

Claims 2-5 and 7-18 are generic to any group paid for.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical feature that distinguishes each group lies in the B substituent which is different in structure in each of the four groups and none of which are known as equivalents in the art.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/47, 31/445, C07D 217/26, 401/12, 471/04

A1

(11) International Publication Number: **WO 99/64002**

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(21) International Application Number: PCT/US99/13252

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(30) Priority Data:

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9817179.6	6 August 1998 (06.08.98)	GB
60/123,260	8 March 1999 (08.03.99)	US

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(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SPIROPIPERIDINE DERIVATIVES AS MELANOCORTIN RECEPTOR AGONISTS

(57) Abstract

Certain novel spiropiperidine compounds are agonists of melanocortin receptor(s) and are useful for the treatment, control or prevention of diseases and disorders responsive to the activation of melanocortin receptors. The compounds of the present invention are therefore useful for treatment of diseases and disorders such as obesity, diabetes, sexual dysfunction including erectile dysfunction and female sexual dysfunction.

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TITLE OF THE INVENTION

SPIROPIPERIDINE DERIVATIVES AS MELANOCORTIN RECEPTOR AGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is based on, and claims priority from, provisional applications 60/08890 filed June 11, 1998, and 60/12326 filed March 8, 1999, which are hereby incorporated by reference in their entireties.

SUMMARY OF THE INVENTION

Spiropiperidine derivatives are melanocortin receptor agonists, and as such are useful in the treatment of disorders responsive to the activation of melanocortin receptors, such as obesity, diabetes as well as male and/or female sexual dysfunction.

BACKGROUND OF THE INVENTION

Pro-opiomelanocortin (POMC) derived peptides are known to affect food intake. Several lines of evidence support the notion that the G-protein coupled receptors (GPCRs) of the melanocortin receptor (MC-R) family, several of which are expressed in the brain, are the targets of POMC derived peptides involved in the control of food intake and metabolism. A specific single MC-R that may be targeted for the control of obesity has not yet been identified.

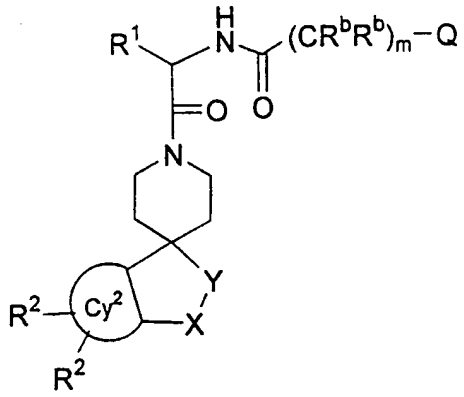
Evidence for the involvement of MC-Rs in obesity includes: i) the agouti (A^{vy}) mouse which ectopically expresses an antagonist of the MC-1R, MC-3R and -4R is obese, indicating that blocking the action of these three MC-Rs can lead to hyperphagia and metabolic disorders; ii) MC-4R knockout mice (Huszar et al., Cell, 88, 131-141, 1997) recapitulate the phenotype of the agouti mouse and these mice are obese; iii) the cyclic heptapeptide MT-II (MC-1R, -3R, -4R, -5R, agonist) injected intracerebroventricularly (ICV) in rodents, reduces food intake in several animal feeding models (NPY, *ob/ob*, agouti, fasted) while ICV injected SHU-9119 (MC-3R, -4R antagonist; MC-1R and -5R agonist) reverses this effect and can induce hyperphagia; iv) chronic intraperitoneal treatment of Zucker fatty rats with an α-NDP-MSH derivative (HP228) has been reported to activate MC-1R, -3R, -4R and -5R and to attenuate food intake and body weight gain over a 12 week period.

Five MC-Rs have thus far been identified, and these are expressed in different tissues. MC-1R was initially characterized by dominant gain of function mutations at the Extension locus, affecting coat color by controlling phaeomelanin to eumelanin conversion through control of tyrosinase. MC-1R is mainly expressed in melanocytes. MC-2R is expressed in the adrenal gland and represents the ACTH receptor. MC-3R is expressed in the brain, gut and placenta and may be involved in the control of food intake and thermogenesis. MC-4R is uniquely expressed in the brain and its inactivation was shown to cause obesity. MC-5R is expressed in many tissues including white fat, placenta and exocrine glands. A low level of expression is also observed in the brain. MC-5R knock out mice reveal reduced sebaceous gland lipid production (Chen et al., Cell, 1997, 91, 789-798).

Intramuscular administration of the MC-1R, -3R, -4R, -5R agonist, melanotan -II (MT-II; 0.005 - 0.03 mg/kg; Dorr et al., Life Sciences, vol. 58, # 20, 1777-1784, 1996) caused intermittent non-painful penile erections in three normal male volunteers for a period of 1-5 hours after dosing. Intramuscular administration of MT-II (0.025 mg/kg and 0.1 mg/kg) to 10 non-organic impotent patients caused transient erections (8 responders) with onset from 50-180 minutes; penile erections subsided after ejaculation (15th American Peptide Symposium 6/14-19, 1997, Nashville, TN, study now published in J. Urology, 160, 389-393, 1998).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds having the formula I:

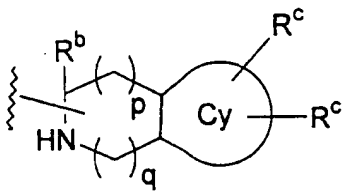


I

wherein

Cy2 is a six-membered aromatic ring containing 0 or 1 N atom or cyclohexane;

Q is



;

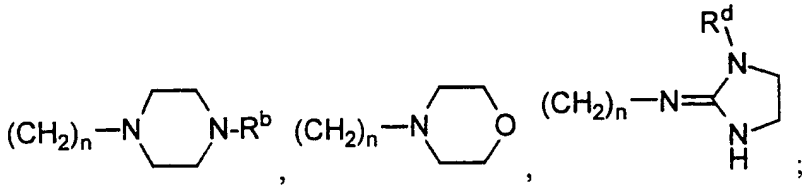
X is O, CH_2, SO_2, $CHCO_2R^b$, $CHSO_2R^a$, $CHC(O)N(R^b)_2$, NR^b, NSO_2R^a, $NSO_2N(R^b)_2$, $NCOR^a$, $NCON(R^b)_2$, $CHN(R^b)COR^a$, $CHN(R^b)SO_2R^a$, $CHCH_2OR^b$, or $CH(CH_2)$-heteroaryl;

Y is $(CH_2)_r$, CH-C_{1-8}alkyl, O, C=O or SO_2, with the proviso that when Y is O, the ring atom of X is carbon;

R^1 is H, C_{1-8}alkyl, $CH(R^b)$-aryl, $CH(R^b)$-heteroaryl, $(CH_2)_n$-C_{5-6}cycloalkyl in which aryl and heteroaryl are optionally substituted by one or two R^c groups;

R^2 is H or halo;

R^a is R^b, $(CH_2)_nN(R^b)_2$, $(CH_2)_nN(R^b)C(=NR^d)NR^b$, $(CH_2)_n$NH-2-pyridyl, $(CH_2)_n$NH-2-imidazolyl, $(CH_2)_n$NH-2-thiazolyl, $(CH_2)_n$NH-2-pyrimidinyl,



;

R^b is H, C_{1-8}alkyl, $(CH_2)_n$aryl, $(CH_2)_n$heteroaryl, C_{3-6}cycloalkyl; or 2 R^b together with the nitrogen atom to which they are attached form a 5- or 6-membered ring optionally containing an additional heteroatom selected from O, S, and NR^1;

R^c is R^b, halo, OR^b, $NHSO_2R^b$, $N(R^b)_2$, CN, NO_2, $SO_2N(R^b)_2$, SO_2R^b, CF_3, OCF_3; or two R^c groups attached to adjacent carbon atoms together form methylenedioxy;

R^d is H, NO_2, or CN;

Cy is aryl, 5- or 6-membered heteroaryl, 5- or 6-membered heterocyclyl, or 5-or 6-membered carbocyclyl;

n is 0 to 3;

m, p and q are independently 0, 1 or 2;

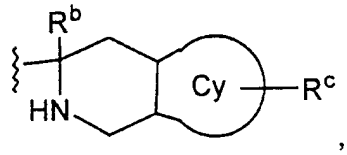
r is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

In one subset of compounds of formula I are compounds wherein Cy^2 is benzene or cyclohexane.

In another subset of compounds of formula I are compounds wherein X is $CHCO_2R^b$, $CHC(O)N(R^b)_2$, NSO_2R^a, $CHN(R^b)COR^a$, $CHN(R^b)SO_2R^a$, $CHCH_2OR^b$ or $CHCH_2$-heteroaryl.

In another subset of compounds of formula I are compounds wherein Q is

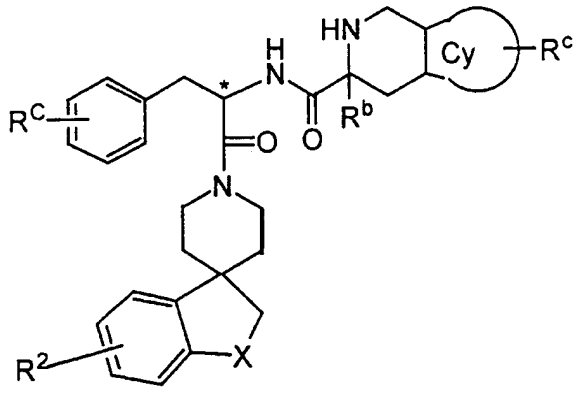


,

R^b and R^c are as defined under formula I, and Cy is aryl, 5- or 6-membered heteroaryl, or 5-or 6-membered carbocyclyl. Preferably Cy is benzene or cyclohexane.

In another subset of compounds of formula I are compounds wherein R^1 is CH_2-aryl in which aryl is optionally substituted by R^c.

In a preferred embodiment there are provided compounds of formula Ia:

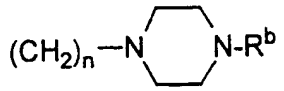
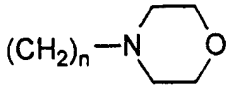


Ia

wherein

X is $CHCO_2R^b$, $CHC(O)N(R^b)_2$, NSO_2R^a, $CHN(R^b)COR^a$, or $CHN(R^b)SO_2R^a$;

R^2 is H or halo;

R^a is R^b, $(CH_2)_nN(R^b)_2$, $(CH_2)_n$NH-2-pyridyl, $(CH_2)_n$NH-2-imidazolyl,  , $(CH_2)_n$NH-2-thiazolyl, $(CH_2)_n$NH-2-pyrimidinyl,  ;

R^b is H, C_{1-8}alkyl, $(CH_2)_n$aryl, $(CH_2)_n$heteroaryl, or C_{3-6}cycloalkyl;

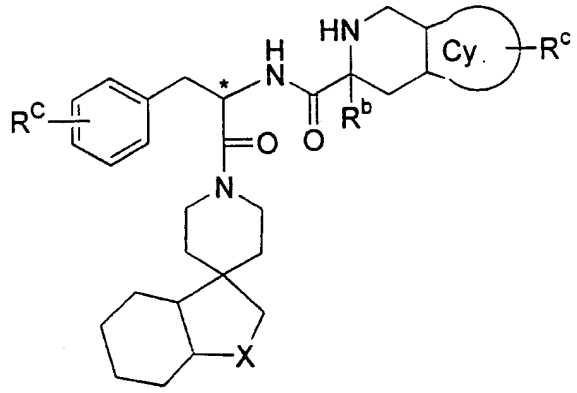
R^c is H, halo, R^b, OR^b, CF_3, OCF_3;

Cy is benzene, pyridine, imidazole or cyclohexane;

n is 0 to 3;

or a pharmaceutically acceptable salt thereof.

In another preferred embodiment are compounds of the formula Ib:



Ib

wherein

X is $CHCO_2R^b$, $CHC(O)N(R^b)_2$, $CHCH_2OR^b$ or $CHCH_2$-heteroaryl;

R^b is H, C_{1-8}alkyl, $(CH_2)_n$aryl, $(CH_2)_n$heteroaryl, or C_{3-6}cycloalkyl;

R^c is H, halo, R^b, OR^b, CF_3, OCF_3;

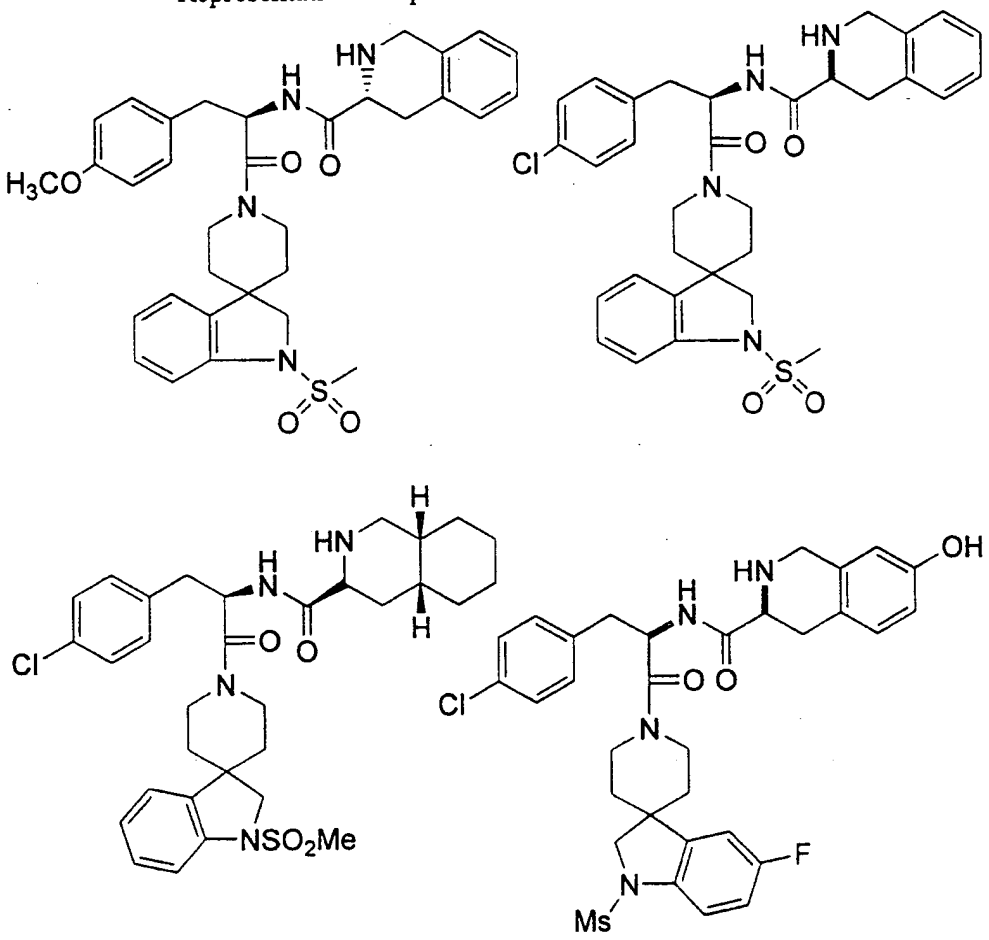
Cy is benzene, pyridine, imidazole or cyclohexane;

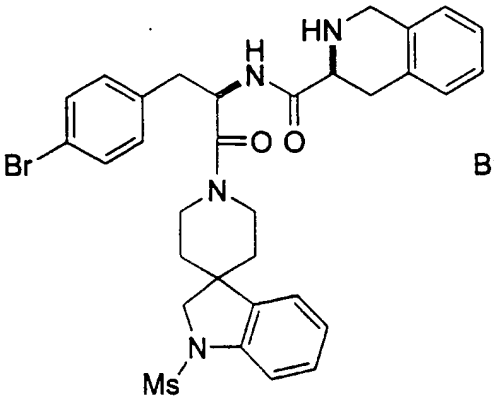
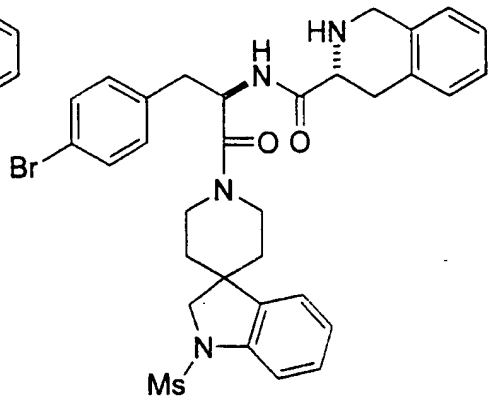
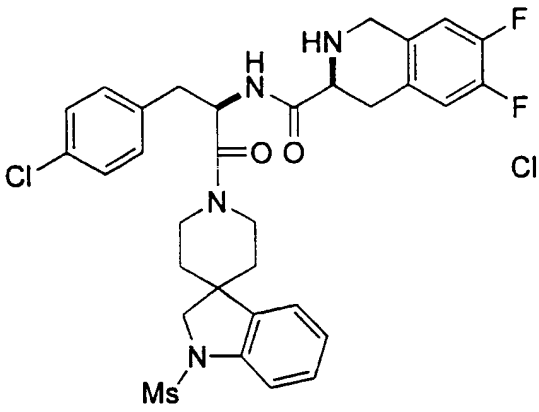
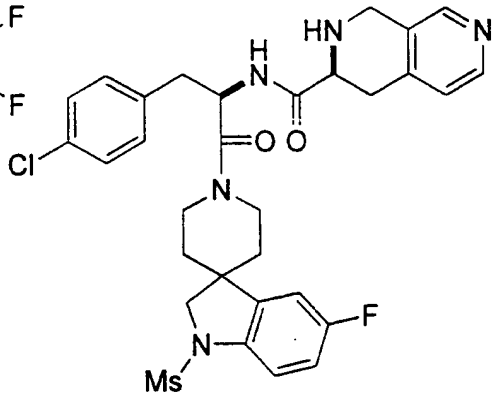
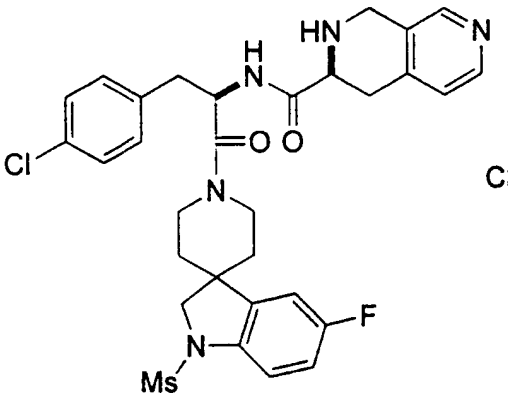
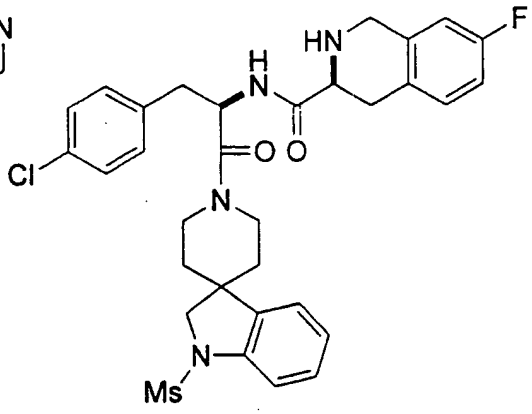
n is 0 to 3;

or a pharmaceutically acceptable salt thereof.

In a more preferred embodiment of compounds of formulas Ia and Ib, the carbon atom marked with * has the *R* configuration. In another more preferred embodiment of formulas Ia and Ib Cy is benzene or cyclohexane.

Representative compounds of formula I are as follows:



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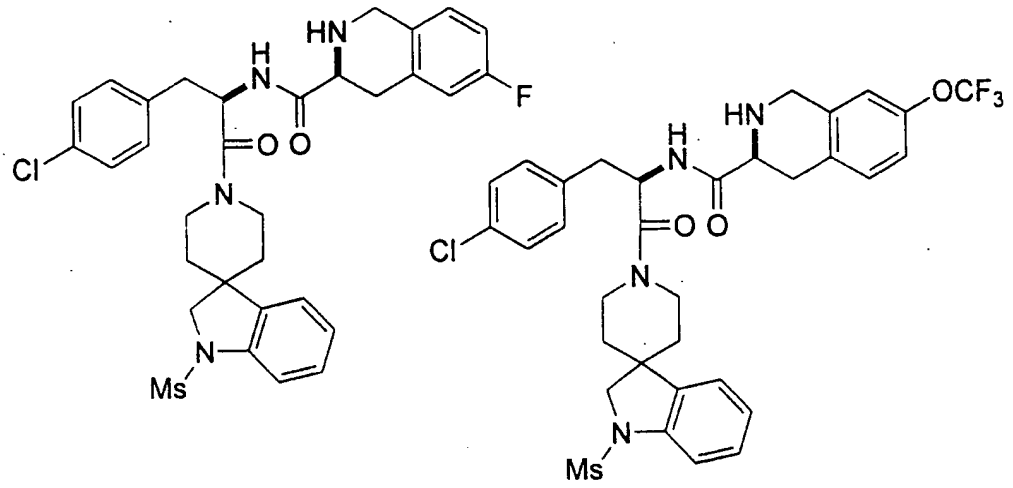
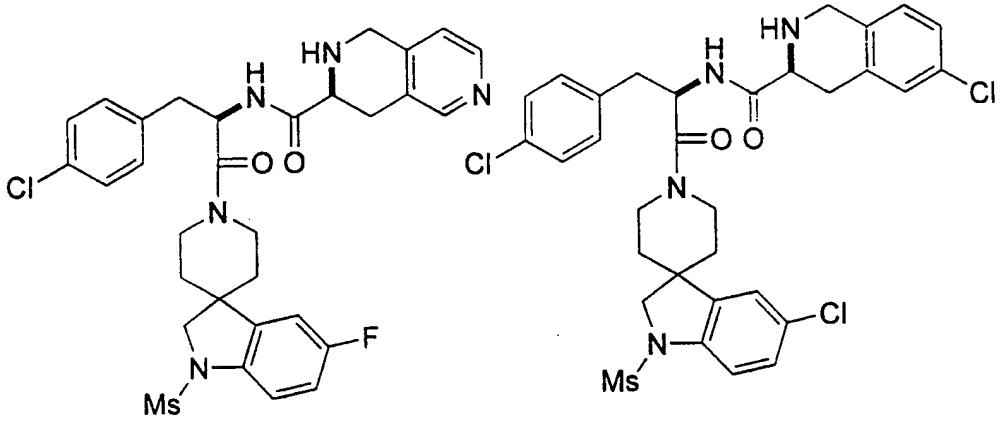
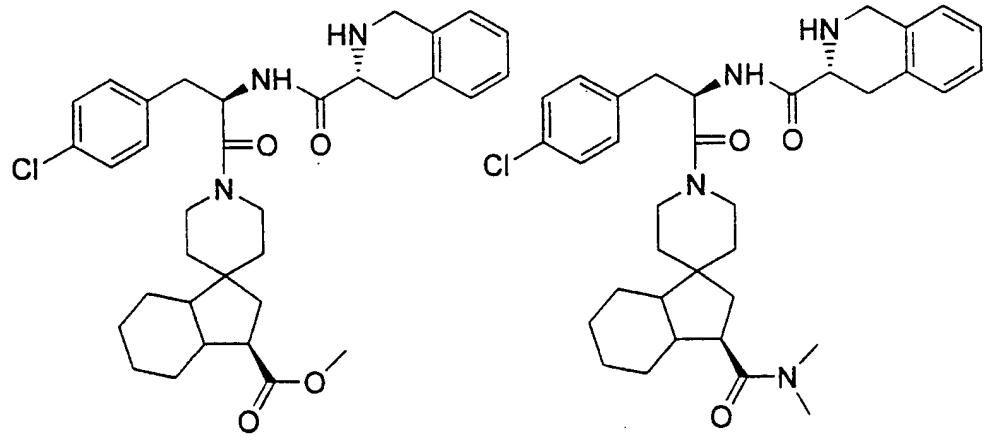
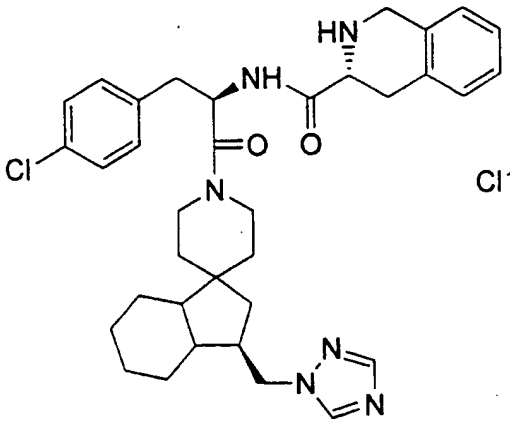
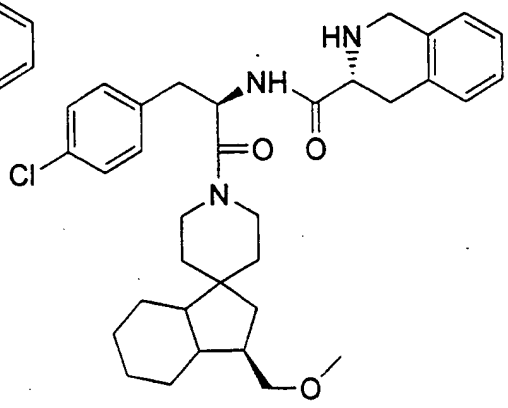
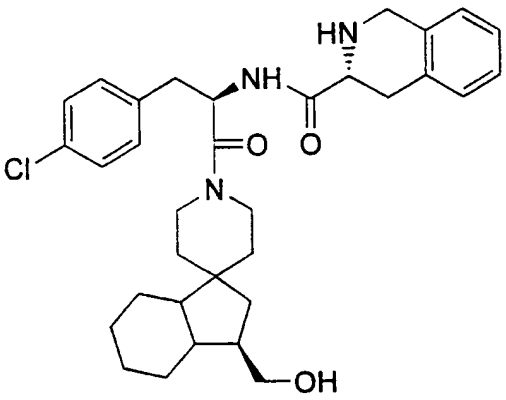












Another aspect of the present invention provides a method for the treatment or prevention of obesity or diabetes in a mammal which comprises administering to said mammal an effective amount of a compound of formula I.

Another aspect of the present invention provides a method for the treatment or prevention of male or female sexual dysfunction including erectile dysfunction which comprises administering to a patient in need of such treatment or prevention an effective amount of a compound of formula I.

Another aspect of the present invention provides a method for the treatment or prevention of male or female sexual dysfunction including erectile dysfunction which comprises administering to a patient in need of such treatment or prevention an effective amount of an agonist of melanocortin-4 receptor.

Yet another aspect of the present invention provides a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier.

Throughout the instant application, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term "aryl" includes phenyl and naphthyl.

The term "heteroaryl" includes mono- and bicyclic aromatic rings containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. "5- or 6-membered heteroaryl" are monocyclic heteroaromatic rings, examples thereof include thiazole, oxazole, thiophene, furan, pyrrole, imidazole, isoxazole, pyrazole, triazole, thiadiazole, tetrazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, and the like. Bicyclic heteroaromatic rings include, but are not limited to, benzothiadiazole, indole, benzothiophene, benzofuran, benzimidazole, benzisoxazole, benzothiazole, quinoline, benzotriazole, benzoxazole, isoquinoline, purine, furopyridine and thienopyridine.

The term "5- or 6-membered carbocyclyl" is intended to include non-aromatic rings containing only carbon atoms such as cyclopentyl and cyclohexyl.

The term "5 and 6-membered heterocyclyl" is intended to include non-aromatic heterocycles containing one to four heteroatoms selected from nitrogen, oxygen and sulfur. Examples of a 5 or 6-membered heterocyclyl include piperidine, morpholine, thiamorpholine, pyrrolidine, imidazolidine, tetrahydrofuran, piperazine, and the like.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus for example, NR^bR^b may represent NH_2, $NHCH_3$, $N(CH_3)CH_2CH_3$, and the like.

The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s)

that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

"Erectile dysfunction" is a disorder involving the failure of a male mammal to achieve erection, ejaculation, or both. Symptoms of erectile dysfunction include an inability to achieve or maintain an erection, ejaculatory failure, premature ejaculation, inability to achieve an orgasm. An increase in erectile dysfunction is often associated with age and is generally caused by a physical disease or as a side-effect of drug treatment.

"Female sexual dysfunction" encompasses, without limitatin, conditions usch as a lack of sexual desire and related arousal disorders, inhibited orgasm, lubrication difficulties, and vaginismus.

Abbreviations Used

9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
BOC (boc)	t-butyloxycarbonyl
BOP	benzotriazol-1-yloxy tris(dimethylamino) phosphonium hexafluorophosphate
Bu	butyl
calc.	calculated
CBZ (Cbz)	benzyloxycarbonyl
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DIEA	diisopropylethylamine
DMAP	4-(N,N-dimethylamino)pyridine
DMF	dimethylformamide
DPPA	diphenylphosphoryl azide
EDC	1-(3-dimethylaminopropyl)3-ethylcarbodiimide HCl
eq.	equivalent(s)
ESI-MS	electron ion-mass spectroscopy

EtOAc	ethyl acetate
FAB-MS	fast atom bombardment-mass spectroscopy
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high pressure liquid chromatography
KHDMS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LHMDS	lithium bis(trimethylsilyl)amide
MC-*x*R	melanocortin receptor (*x* being a number)
Me	methyl
MF	molecular formula
MHz	megahertz
MPLC	medium pressure liquid chromatography
Ms	methanesulfonyl
NMM	N-methylmorpholine
NMR	nuclear magnetic resonance
PCC	pyridium chlorochromate
Ph	phenyl
Pr	propyl
prep.	prepared
PyBrop	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tic	1,2,3,4-tetrahydroisoquinoline-3- carboxylic acid
TLC	thin-layer chromatography
TMS	tetramethylsilane

Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of Formula I contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent.

Alternatively, any enantiomer of a compound of the general Formula I or Ia may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic,

citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Particularly preferred are citric, fumaric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utility

Compounds of formula I are melanocortin receptor agonists and as such are useful in the treatment, control or prevention of diseases, disorders or conditions responsive to the activation of one or more of the melanocortin receptors including, but are not limited to, MC-1, MC-2, MC-3, MC-4, or MC-5. Such diseases, disorders or conditions include, but are not limited to, obesity (by reducing appetite, increasing metabolic rate, reducing fat intake or reducing carbohydrate craving), diabetes mellitus (by enhancing glucose tolerance, decreasing insulin resistance), hypertension, hyperlipidemia, osteoarthritis, cancer, gall bladder disease, sleep apnea, depression, anxiety, compulsion, neuroses, insomnia/sleep disorder, substance abuse, pain, male and female sexual dysfunction (including impotence, loss of libido and erectile dysfunction), fever, inflammation, immune modulation, rheumatoid arthritis, skin tanning, acne and other skin disorders, neuroprotective and cognitive and memory enhancement including the treatment of Alzheimer's disease. Some compounds of formula I show highly specific activity toward the melanocortin-4 receptor which makes them especially useful in the prevention and treatment of obesity, as well as male and female sexual dysfunction.

Administration and Dose Ranges

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of Formula I are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from 0.01 milligram to about 100 milligrams per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.7 milligrams to about 3500 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

When treating diabetes mellitus and/or hyperglycemia, as well as other diseases or disorders for which compounds of formula I are useful, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.001 milligram to about 100 milligram per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.07 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

For the treatment of sexual dysfunction compounds of the present invention are given in a dose range of 0.001 milligram to about 100 milligram per kilogram of body weight, preferably as a single dose orally or as a nasal spray.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose

or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

Combination Therapy

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that

may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

(a) insulin sensitizers including (i) PPARγ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin;

(b) insulin or insulin mimetics;

(c) sulfonylureas such as tolbutamide and glipizide;

(d) α-glucosidase inhibitors (such as acarbose),

(e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin and pravastatin, fluvastatin, atorvastatin, and other statins), (ii) sequestrants (cholestyramine, colestipol and a dialkylaminoalkyl derivatives of a cross-linked dextran), (ii) nicotinyl alcohol nicotinic acid or a salt thereof, (iii) proliferator-activater receptor α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrat, fenofibrate and benzafibrate), (iv) inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide, (v) probucol, (vi) vitamin E, and (vii) thyromimetics;

(f) PPARδ agonists such as those disclosed in WO97/28149;

(g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, or β3 adrenergic receptor agonists;

(h) feeding behavior modifying agents such as neuropeptide Y antagonists (e.g. neuropeptide Y5) such as those disclosed in WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822 and WO 97/20823;

(i) PPARα agonists such as described in WO 97/36579 by Glaxo;

(j) PPARγ antagonists as described in WO97/10813;

(k) serotonin reuptake inhibitors such as fluoxetine and sertraline;

(l) growth hormone secretagogues such as MK-0677; and

(m) agents useful in the treatment of male and/or female sexual dysfunction such as phosphodiester V inhibitors such as sildenafil, and α-2 adrenergic receptor antagonists.

Biological Assays

A. Binding Assay. The membrane binding assay is used to identify competitive inhibitors of ^{125}I-α-NDP-MSH binding to cloned human MCRs expressed in L- or CHO- cells.

Cell lines expressing melanocortin receptors are grown in T-180 flasks containing selective medium of the composiiton: 1 L Dulbecco's modified Eagles Medium (DMEM) with 4.5 g L-glucose, 25 mM Hepes, without sodium pyruvate, (Gibco/BRl); 100 ml 10% heat-inactivated fetal bovine serum (Sigma); 10 ml 10,000 unit/ml penicillin & 10,000 ug/ml streptomycin (Gibco/BRl); 10 ml 200 mM L-glutamine (Gibco/BRl); 1 mg/ml Geneticin (G418) (Gibco/BRl). The cells are grown at 37°C with CO_2 and humidity control until the desired cell density and cell number is obtained

The medium is poured off and 10 mls/monolayer of enzyme-free dissociation media (Specialty Media Inc.) is added. The cells are incubated at 37°C for 10 minutes or until cells slough off when flask is banged against hand.

The cells are harvested into 200 ml centrifuge tubes and spun at 1000 rpm, 4° C, for 10 min. The supernatant is discarded and the cells are resuspended in 5 mls/monolayer membrane preparation buffer having the composition: 10 mM Tris pH 7.2-7.4; 4 ug/ml Leupeptin (Sigma); 10 uM Phosphoramidon (Boehringer Mannheim); 40 ug/ml Bacitracin (Sigma); 5 ug/ml Aprotinin (Sigma); 10 mM Pefabloc (Boehringer Mannheim). The cells are homogenized with motor-driven dounce (Talboy setting 40), using 10 strokes and the homogenate centrifuged at 6,000 rpm, 4 C, for 15 minutes.

The pellets are resuspended in 0.2 mls/monolayer membrane prep buffer and aliquots are placed in tubes (500-1000 ul/tube) and quick frozen in liquid nitrogen and then store at -80 ° C.

Test compounds or unlabelled NDP-α-MSH is added to 100 µL of membrane binding buffer to a final concentration of 1 µM. The membrane binding buffer has the composition: 50 mM Tris pH 7.2; 2 mM CaCl2; 1 mM MgCl2; 5 mM KCl; 0.2% BSA; 4 ug/ml Leupeptin (SIGMA); 10 uM Phosphoramidon (Boehringer Mannheim); 40 ug/ml Bacitracin (SIGMA); 5 ug/ml Aprotinin (SIGMA); and 10 mM Pefabloc (Boehringer Mannheim). One hundred µl of membrane binding buffer containing 10-40 ug membrane protein is added, followed by 100 µM 125I-NDP-α-

MSH to final concentration of 100 pM. The resulting mixture is vortexed briefly and incubated for 90-120 min at room temp while shaking.

The mixture is filtered with Packard Microplate 196 filter apparatus using Packard Unifilter 96-well GF/C filter with 0.1% polyethyleneimine (Sigma). The filter is washed (5 times with a total of 10 ml per well) with room temperature of filter wash having the composition: 50mM Tris-HCl pH 7.2 and 20 mM NaCl. The filter is dried, and the bottom sealed and 50 ul of Packard Microscint-20 is added to each well. The top is sealed and the radioactivity quantitated in a Packard Topcount Microplate Scintillation counter.

B. Functional assay. Functional cell based assays are developed to discriminate agonists and antagonists.

Cells (for example, CHO- or L-cells or other eukaryotic cells) expressing a human melanocortin receptor (see e.g. Yang-YK; Ollmann-MM; Wilson-BD; Dickinson-C; Yamada-T; Barsh-GS; Gantz-I; Mol-Endocrinol. 1997 Mar; 11(3): 274-80) are dissociated from tissue culture flasks by rinsing with Ca and Mg free phosphate buffered saline (14190-136, Life Technologies, Gaithersburg, MD) and detached following 5 minutes incubation at 37°C with enzyme free dissociation buffer (S-014-B, Specialty Media, Lavellette, NJ). Cells are collected by centrifugation and resuspended in Earle's Balanced Salt Solution (14015-069, Life Technologies, Gaithersburg, MD) with additions of 10 mM HEPES pH 7.5, 5 mM $MgCl_2$, 1 mM glutamine and 1 mg/ml bovine serum albumin. Cells are counted and diluted to 1 to 5 x 10^6/ml. The phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine is added to cells to 0.6 mM.

Test compounds are diluted in dimethylsulfoxide (DMSO) (10^{-5} to 10^{-10} M) and 0.1 volume of compound solution is added to 0.9 volumes of cell suspension; the final DMSO concentration is 1%. After room temperature incubation for 45 min., cells are lysed by incubation at 100 C for 5 min. to release accumulated cAMP.

cAMP is measured in an aliquot of the cell lysate with the Amersham (Arlington Heights, IL) cAMP detection assay (RPA556). The amount of cAMP production which results from an unknown compound is compared to that amount of cAMP produced in response to alpha-MSH which is defined as a 100 % agonist. The

EC_{50} is defined as the compound concentration which results in half maximal stimulation, when compared to its own maxim level of stimulation.

Antagonist assay: Antagonist activity is defined as the ability of a compound to block cAMP production in response to alpha-MSH. Solution of test compounds and suspension of receptor containing cells are prepared and mixed as described above; the mixture is incubated for 15 min., and an EC50 dose (approximately 10 nM alpha-MSH) is added to the cells. The assay is terminated at 45 min. and cAMP quantitated as above. Percent inhibition is determined by comparing the amount of cAMP produced in the presence to that produced in the absence of test compound.

C. In vivo food intake models.

1) Overnight food intake. Sprague Dawley rats are injected intracerebroventricularly with a test compound in 400 nL of 50% propylene glycol/artificial cerebrospinal fluid one hour prior to onset of dark cycle (12 hours). Food intake is determined using a computerized system in which each rat's food is placed on a computer monitored balance. Cumulative food intake for 16 hours post compound administration is measured.

2) Food intake in diet induced obese mice. Male C57/B16J mice maintained on a high fat diet (60% fat calories) for 6.5 months from 4 weeks of age are are dosed intraperitoneally with test compound. Food intake and body weight are measured over an eight day period. Biochemical parameters relating to obesity, including leptin, insulin, triglyceride, free fatty acid, cholesterol and serum glucose levels are determined.

D. Rat Ex Copula Assay

Sexually mature male Caesarian Derived Sprague Dawley (CD) rats (over 60 days old) are used with the suspensory ligament surgically removed to prevent retraction of the penis back into the penile sheath during the ex copula evaluations. Animals receive food and water *ad lib* and are kept on a normal light/dark cycle. Studies are conducted during the light cycle.

a) Conditioning to Supine Restraint for Ex Copula Reflex Tests. This conditioning takes ~ 4 days. Day 1, the animals are placed in a darkened restrainer and left for 15 - 30 minutes. Day 2, the animals are restrained in a supine position in the restrainer for 15 - 30 minutes. Day 3, the animals are restrained in the supine position with the penile sheath retracted for 15 - 30 minutes. Day 4, the animals are restrained in the supine position with the penile sheath retracted until penile responses are observed. Some animals require additional days of conditioning before they are completely acclimated to the procedures; non-responders are removed from further evaluation. After any handling or evaluation animals are given a treat to ensure positive reinforcement.

b) Ex Copula Reflex Tests. Rats are gently restrained in a supine position with their anterior torso placed inside a cylinder of adequate size to allow for normal head and paw grooming. For a 400-500 gram rat, the diameter of the cylinder is approximately 8 cm. The lower torso and hind limbs are restrained with a non-adhesive material (vetrap). An additional piece of vetrap with a hole in it, through which the glans penis will be passed, is fastened over the animal to maintain the preputial sheath in a retracted position. Penile responses will be observed, typically termed *ex copula* genital reflex tests. Typically, a series of penile erections will occur spontaneously within a few minutes after sheath retraction. The types of normal reflexogenic erectile responses include elongation, engorgement, cup and flip. An elongation is classified as an extension of the penile body. Engorgement is a dilation of the glans penis. A cup is defined as an intense erection where the distal margin of the glans penis momentarily flares open to form a cup. A flip is a dorsiflexion of the penile body.

Baseline and or vehicle evaluations are conducted to determine how and if an animal will respond. Some animals have a long duration until the first response while others are non-responders altogether. During this baseline evaluation latency to first response, number and type of responses are recorded. The testing time frame is 15 minutes after the first response.

After a minimum of 1 day between evaluations, these same animals are administered the test compound at 20 mg/kg and evaluated for penile reflexes. All evaluations are videotaped and scored later. Data are collected and analyzed using paired 2 tailed t-tests to compared baseline and/ or vehicle evaluations to drug treated

evaluations for individual animals. Groups of a minimum of 4 animals are utilized to reduce variability.

Positive reference controls are included in each study to assure the validity of the study. Animals can be dosed by a number of routes of administration depending on the nature of the study to be performed. The routes of administration includes intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and intracerebral ventricular (ICV).

E. Models of Female Sexual Dysfunctioin

Rodent assays relevant to female sexual receptivity include the behavioral model of lordosis and direct observations of copulatory activity. There is also a urethrogenital reflex model in anesthetized spinally transected rats for measuring orgasm in both male and female rats. These and other established animal models of female sexual dysfunction are described in McKenna KE et al, A Model For The Study Of Sexual Function In Anesthetized Male And Female Rats, Am. J. Physiol. (Regulatory Integrative Comp. Physiol 30): R1276-R1285, 1991; McKenna KE et al, Modulation By Peripheral Serotonin Of The Threshold For Sexual Reflexes In Female Rats, Pharm. Bioch. Behav., 40:151-156, 1991; and Takahashi LK et al, Dual Estradiol Action In The Diencephalon And The Regulation Of Sociosexual Behavior In Female Golden Hamsters, Brain Res., 359:194-207, 1985.

Preparation of Compound of the Invention

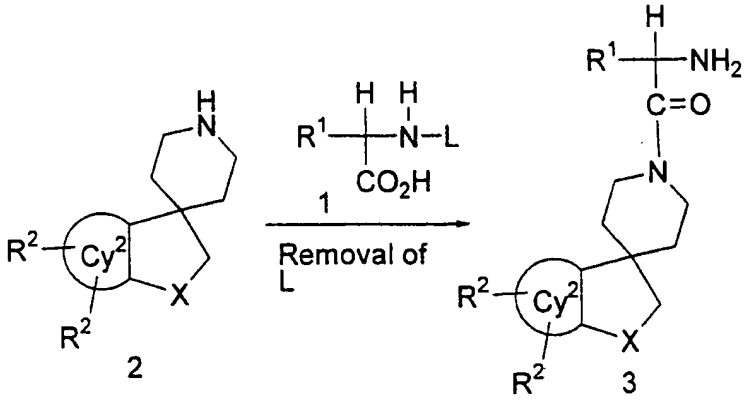
The preparation of compounds of Formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the following reaction schemes. The instant compounds are generally isolated in the form of their pharmaceutically acceptable salts, such as those described previously hereinabove.

The phrase "standard peptide coupling reaction conditions" is used repeatedly here, and it means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The uses of protective groups for amine and carboxylic acid to facilitate the desired reaction and minimize undesired reactions are well documented. Conditions required to remove protecting

groups which may be present and can be found in Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY 1991. CBZ and BOC are used extensively in the synthesis, and their removal conditions are known to those skilled in the art. For example, removal of CBZ groups can be achieved by a number of methods known in the art; for example, catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated by the presence of other potentially reactive functionality, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride or methanol or ethyl acetate, with a strong acid, such as trifluoroacetic acid or hydrochloric acid or hydrogen chloride gas.

The protected amino acid derivatives 1 are, in many cases, commercially available, where the protecting group L is, for example, BOC or CBZ groups. Other protected amino acid derivatives 1 can be prepared by literature methods (Williams, R. M. *Synthesis of Optically Active a-Amino Acids*, Pergamon Press: Oxford, 1989). Many of the piperidines of Formula 2 are either commercially available or known in the literature and others can be prepared following literature methods described for analogous compounds. Some of these methods are illustrated in the subsequent schemes. The skills required in carrying out the reaction and purification of the resulting reaction products are known to those in the art. Purification procedures include crystallization, normal phase or reverse phase chromatography.

SCHEME 1

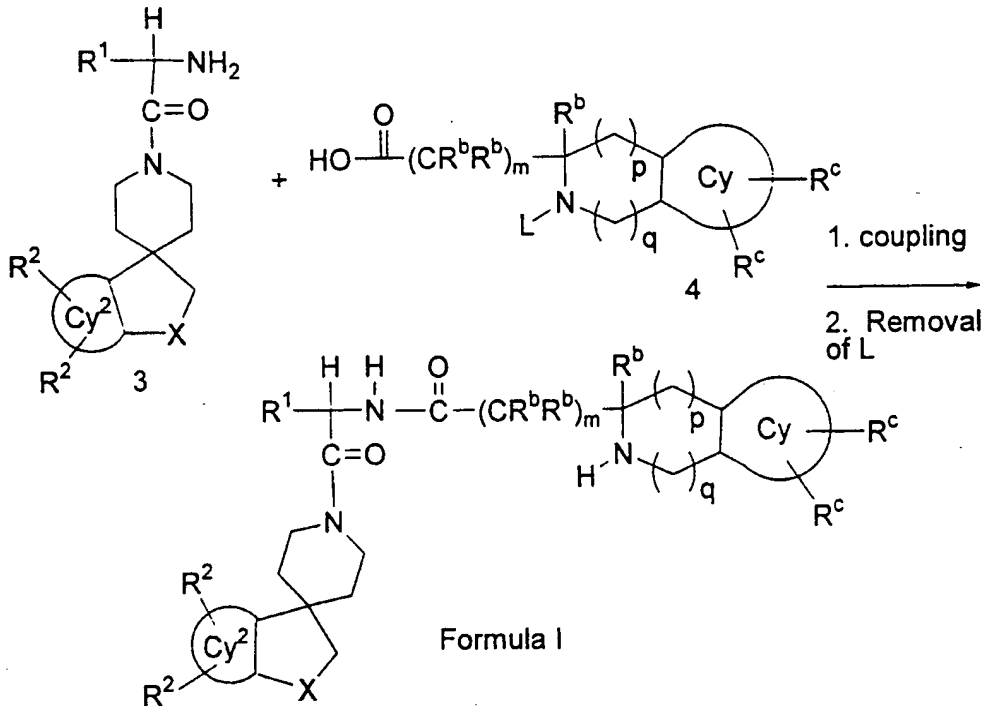


Intermediates of Formula 3 may be synthesized as described in Scheme 1. Coupling of amine of Formula 2 to protected amino acids of Formula 1, wherein L is a suitable protecting group (BOC, CBZ, etc), is conveniently carried out under standard peptide coupling conditions, and the removal of the protecting group may be conducted using well-known methods..

Compounds of Formula I may be prepared as shown in Schemes 2 and 3. In Scheme 2 intermediates of Formula 3 are coupled to protected amino acids of Formula 4 (L = protecting group such as Boc, CBZ, FMOC, etc.) under the standard peptide-type coupling reaction conditions. The amino acids 4 are either commercially available or can be synthesized by methods as described later.

In Scheme 3, amino acid ester intermediates of Formula 5, wherein L' is a small alkyl such as methyl or ethyl or a benzyl or allyl unit, can be synthesized by well documented methods in the literature. Coupling of intermediates 4 and 5 under standard peptide coupling conditions followed by removal of the ester group L' yields the intermediate 6. Compounds of formula I are obtained by coupling intermediates of Formula 6 to spiropiperidines of formula 2 under standard peptide coupling reaction conditions, followed by the removal of the amino protecting group, L.

SCHEME 2

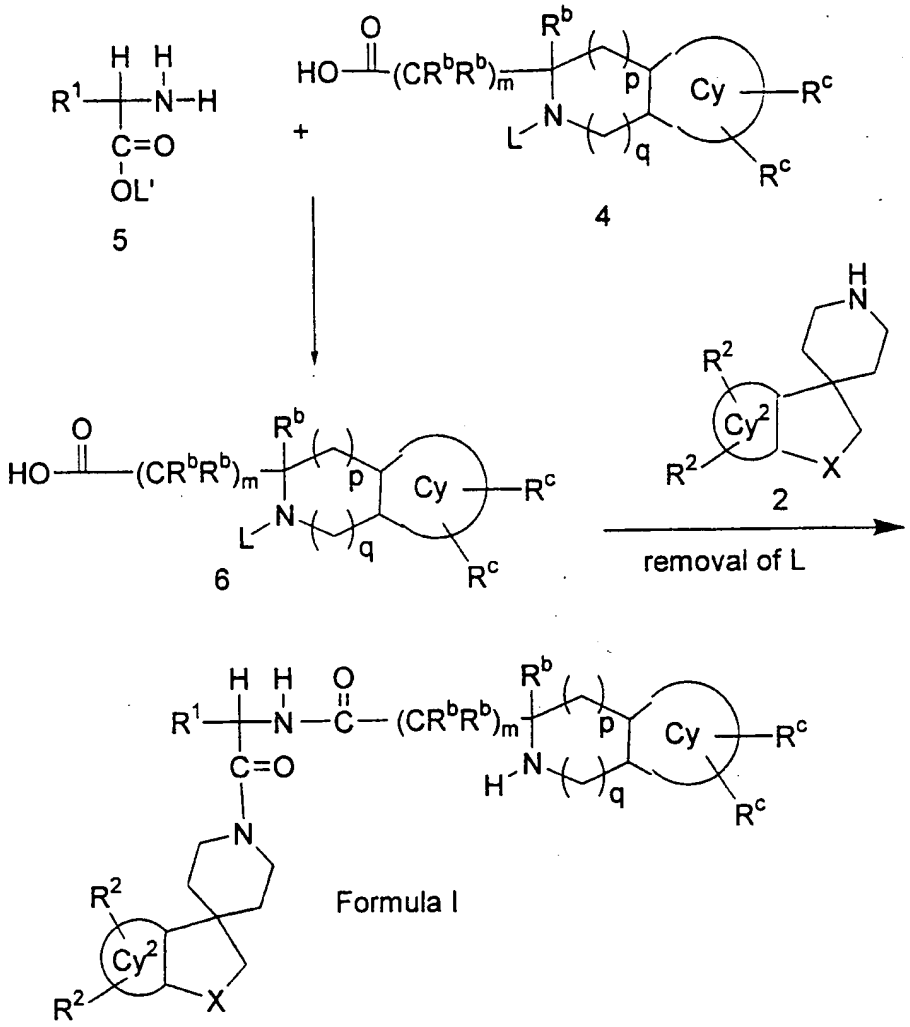


3

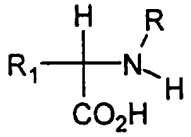
4

Formula I

SCHEME 3



The compounds of the present invention may also be prepared from a variety of substituted natural and unnatural amino acids of formulas 8.



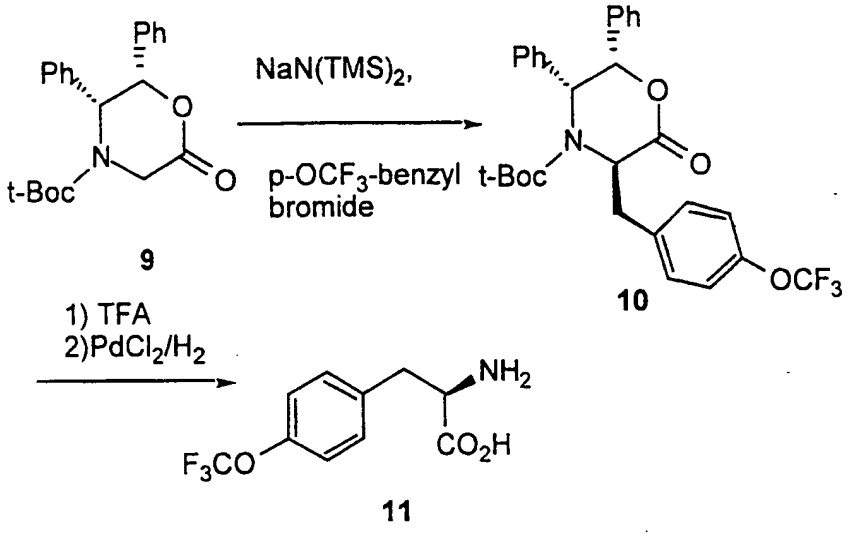
8

The preparation of many of these acids is described in US Patent No. 5,206,237. The preparation of these intermediates in racemic form is accomplished by classical

methods familiar to those skilled in the art (Williams, R. M. "*Synthesis of Optically Active a-Amino Acids*" Pergamon Press: Oxford, 1989; Vol. 7). Several methods exist to resolve (DL)-amino acids. One of the common methods is to resolve amino or carboxyl protected intermediates by crystallization of salts derived from optically active acids or amines. Alternatively, the amino group of carboxyl protected intermediates may be coupled to optically active acids by using chemistry described earlier. Separation of the individual diastereomers either by chromatographic techniques or by crystallization followed by hydrolysis of the chiral amide furnishes resolved amino acids. Similarly, amino protected intermediates may be converted to a mixture of chiral diastereomeric esters and amides. Separation of the mixture using methods described above and hydrolysis of the individual diastereomers provides (D) and (L) amino acids. Finally, an enzymatic method to resolve N-acetyl derivatives of (DL)-amino acids has been reported by Whitesides and coworkers in *J. Am. Chem. Soc.* 1989, 111, 6354-6364.

When it is desirable to synthesize these intermediates in optically pure form, established methods include: (1) asymmetric electrophilic amination of chiral enolates (*J. Am. Chem. Soc.* 1986, 108, 6394-6395, 6395-6397, and 6397-6399), (2) asymmetric nucleophilic amination of optically active carbonyl derivatives, (*J. Am. Chem. Soc.* 1992, 114, 1906; *Tetrahedron Lett.* 1987, 28, 32), (3) diastereoselective alkylation of chiral glycine enolate synthons (*J. Am. Chem. Soc.* 1991, 113, 9276; *J. Org. Chem.* 1989, 54, 3916), (4) diastereoselective nucleophilic addition to a chiral electrophilic glycinate synthon (*J. Am. Chem. Soc.* 1986, 108, 1103), (5) asymmetric hydrogenation of prochiral dehydroamino acid derivatives ("*Asymmetric Synthesis, Chiral Catalysis*; Morrison, J. D., Ed; Academic Press: Orlando, FL, 1985; Vol 5), and (6) enzymatic syntheses (*Angew. Chem. Int. Ed. Engl.* 1978, *17*, 176).

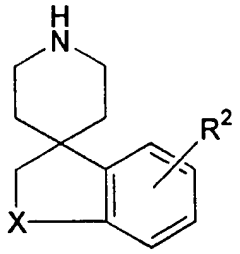
SCHEME 4



9 10 11

For example, alkylation of the enolate of diphenyloxazinone 9 (*J. Am. Chem. Soc.* 1991, 113, 9276) with p-trifluoromethoxybenzyl bromide in the presence of sodium bis(trimethylsilyl)amide proceeds smoothly to afford 10 which is converted into the desired (D)-amino acid 11 by removing the N-t-butyloxycarbonyl group with trifluoroacetic acid and hydrogenation over a $PdCl_2$ catalyst (Scheme 5).

The spiropiperidines of formula 12 may be prepared by a number of methods, including the syntheses described below. In cases where a sulfide is present in the molecule, it may be oxidized to a sulfoxide or to a sulfone with oxidizing agents such as sodium periodate, m-chloroperbenzoic acid or Oxone[®] in an solvent such as dichloromethane, alcohol or water or their mixtures.

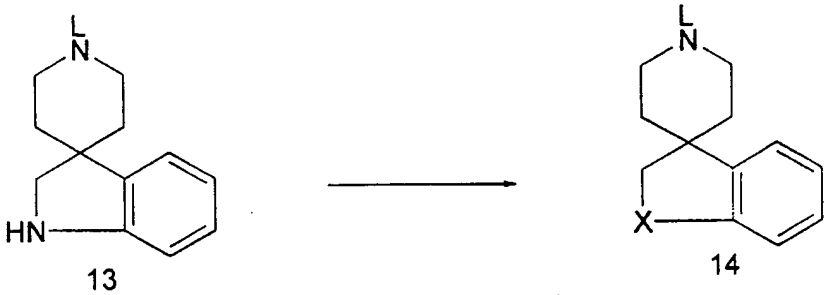


12 X = NR^b, NSO_2R^a, $NSO_2N(R^b)_2$, $NCOR^a$, $NCON(R^b)_2$

As shown in Scheme 5, the spiropiperidine of formula 13, wherein L is a protecting group (such as methyl or benzyl), is synthesized by methods that are known in the literature (for example H. Ong et al *J. Med. Chem.* 1983, *23*, 981-986). The indoline nitrogen of 13 can be reacted by with a variety of electrophiles to yield spiro piperidines of formula 14, wherein the substitutent can be a variety of functionalities, including R^b, SO_2R^a, $SO_2N(R^b)_2$, COR^a, $CON(R^b)_2$. Compound 13 can be reacted with, for example, isocyanates in an inert solvent like dichloromethane to yield urea derivatives, chloroformates in an inert solvent such as dichloromethane to yield carbamates, acid chlorides, anhydrides, or acyl imidazoles to generate amides, sulfonyl chlorides to generate sulfonamides, sulfamyl chlorides to yield sulfamides.

Also, the indoline nitrogen of 13 can be reductively alkylated with aldehydes with conditions known in the art. Aromatic units, including substituted heteroaryl groups, can be introduced by reacting 13 with a fluoro phenyl or fluoro heteroaryl reagent. This chemistry is detailed by H. Ong et al *J. Med. Chem.* 1983, *23*, 981-986.

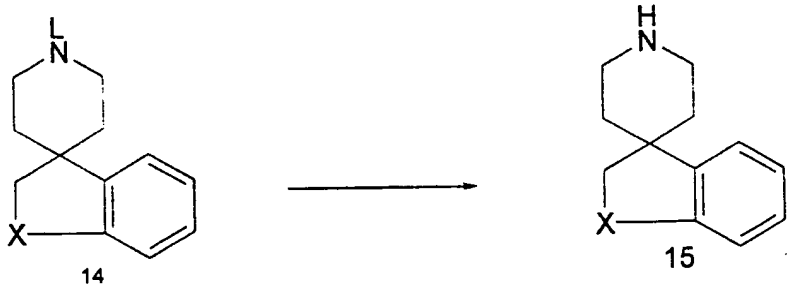
SCHEME 5



As shown in Scheme 6, the spiro piperidine intermediate 14 (L = Me or Bn) can be demethylated or debenzylated using a number of methods well know to those skilled in the art to produce 15. Demethylation of 14 be accomplished by reacting it with cyanogen bromide and potassium carbonate in an inert solvent solvent such as dichloromethane to yield a cyanamide which can reduced to give 15 by

treatment with lithium aluminum hydride in refluxing tetrahydrofuran, refluxing strong acid like aqueous hydrochloric acid, or with Grignard reagents like methyl magnesium bromide. Alternatively, demethylation of 14 can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* 1984, *49*, 2795 and references therein. Debenzylation can be accomplished by reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent like methanol. Alternatively, debenzylation of 14 can be effected with the ACE-Cl method as described in R. Olofson et al. *J. Org. Chem.* 1984, *49*, 2795 and references therein.

SCHEME 6



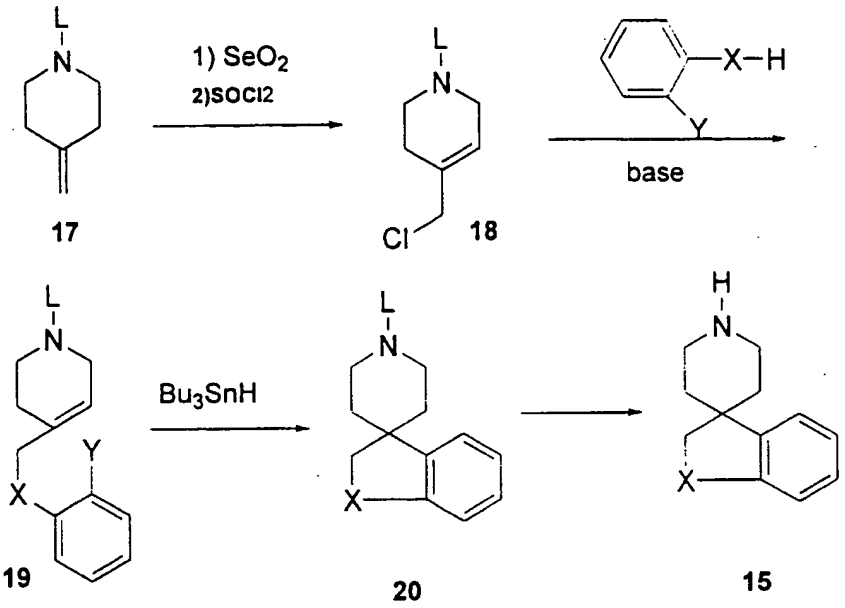
14 15

L = methyl or benzyl

X = NR^b, NSO_2R^a, $NSO_2N(R^b)_2$, $NCOR^a$, $NCON(R^b)_2$

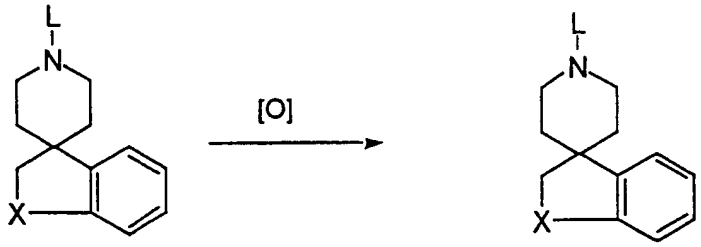
The spiro heterocyclic compounds of formula 15 can be prepared by a number of methods, including the syntheses as described in Scheme 7. Allylic oxidation of the protected piperidine 17 is accomplished by classical methods familiar to those skilled in the art (Rabjohn, N. *Org. React.* 1976, *24*, 261). The resulting allylic alcohol is treated with thionyl chloride in an inert solvent such as benzene to provide the corresponding chloride 18. When X=O or S, the alkylation is carried out in DMF or acetone as solvent with potassium carbonate as a base, and when X = N or derivativized with an alkyl, aryl, acyl, sulfonyl, carbamate) the reaction is carried out with sodium hydride as a base in an inert solvent such as THF to afford the cyclization precursor 19. When L is a defined protecting group, compound 19 can be cyclized by a number methods familiar to those skilled in the art. For example, cyclization of 19 can be accomplished by reaction with tributyltin hydride (Curran , D. P. *Synthesis* 1988, 417 and 489) in an inert solvent such as benzene to yield 16.

SCHEME 7



X = NR^b, NSO_2R^a, $NSO_2N(R^b)_2$, $NCOR^a$, $NCON(R^b)_2$
Y = halide, Se or S

SCHEME 8



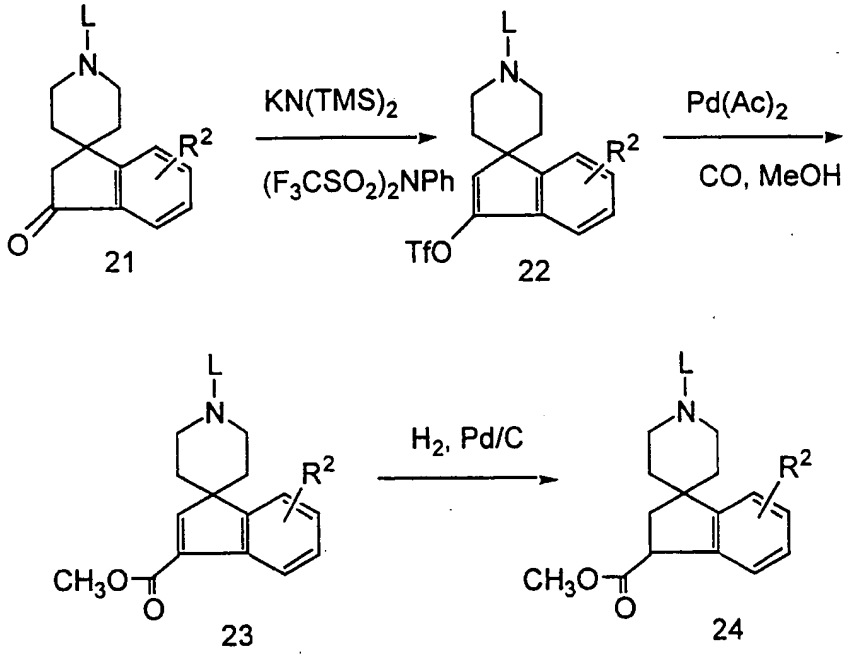
16 X=S

16 X = Sulfoxide or sulfone

As shown in Scheme 8, when X=S, compound 16 can be oxidized to the sulfoxide 16 (X = S(O)) and the sulfone 16 (SO2) by many oxidizing agents. For example, sodium periodate is often used for the synthesis of sulfoxides and Oxone is

used for the synthesis of sulfones. Removal of the protecting group provides the amine 16 which then can be elaborated to melanocortin agonists.

SCHEME 10



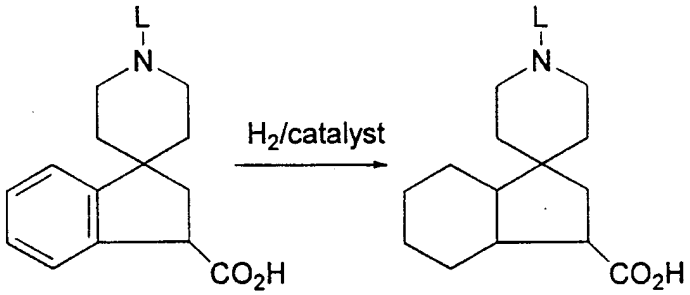
Homologation of the spiroindanone 21 provides easy access to spiroindanyl intermediates containing acid and ester groups. This chemistry is described in Scheme 10. Treatment of 21 with a base in an inert solvent such as THF followed by the addition of a triflating agent provides the enol triflate. Carboxylation of the enol triflate according to the procedure of Cacchi, S. Tetrahedron Letters, 1985, 1109-1112 provides the ester 23. Hydrogenation of 23 using a palladium catalyst in an inert solvent provides the saturated ester 24. The protecting group can then be removed as described above and the resulting amine can be incorporated into the subject compound via the chemistry depicted in earlier schemes.

Saponification of the ester of 24 provides an acid which can be conveniently derivatized as for example reaction with an amine in the presence of a coupling agent such as EDC gives amides. which can then be incorporated into final compounds.

The ester 24 may also be reduced to a primary alcohol with LAH and to a aldehyde with DIBALH. Reductive alkylation of the aldehyde with ammonium acetate and sodium cyanoborohydride affords an amino methyl analog. These aminomethyl analogs may then be further reacted with acylating and sulfonylating agents to afford additional melanocortin compounds of the general formula I.

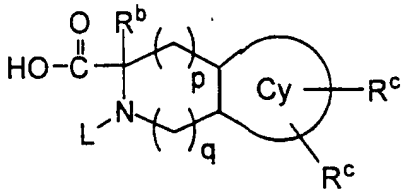
As illustrated in Scheme 11, spiroindanes can be hydrogenated with Pt/C or Rh/alumina as catalysts in solvents such as methanol, ethanol or acetic acid to afford corresponding perhydroindanes. High pressures are often required to carry out this saturation reaction. The L protecting group can be removed by standard methods as discussed above.

SCHEME 11



Chiral acids are available by a variety of methods known to those skilled in the art including asymmetric catalytic hydrogenation and resolution of a pair of diastereomeric salts formed by reaction with a chiral amine such as D or L α-methylbenzylamine. The absolute stereochemistry can be determined in a number of ways including X-ray crystallography of a suitable crystalline derivative.

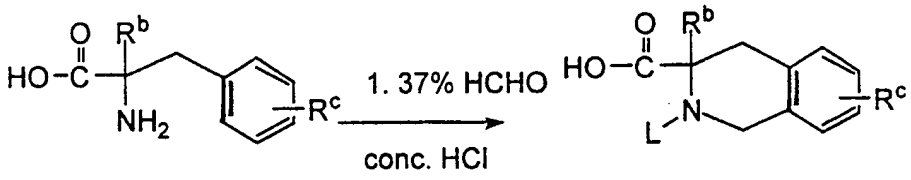
Protected amino acids of formula 5, wherein L is a suitable protecting group such as Boc or CBZ, can by conveniently synthesized by methods well documented in the literature.



5

For example, as shown in Scheme 11, a substituted phenyl alanine derivative 25 can be treated with aqueous formaldehyde in concentrated hydrochloric acid to afford, after protection of the amino functionality in a second step by well documented methods, the tetrahydroisoquinoline compound 26. This reaction can also be effected with heterocyclic amino acids such as 2- and 3-thienyl Ala. Since the above chemistry works generally with retention of stereochemistry, D- and L-amino acids of general formula 5 can be prepared from D- and L- amino acids.

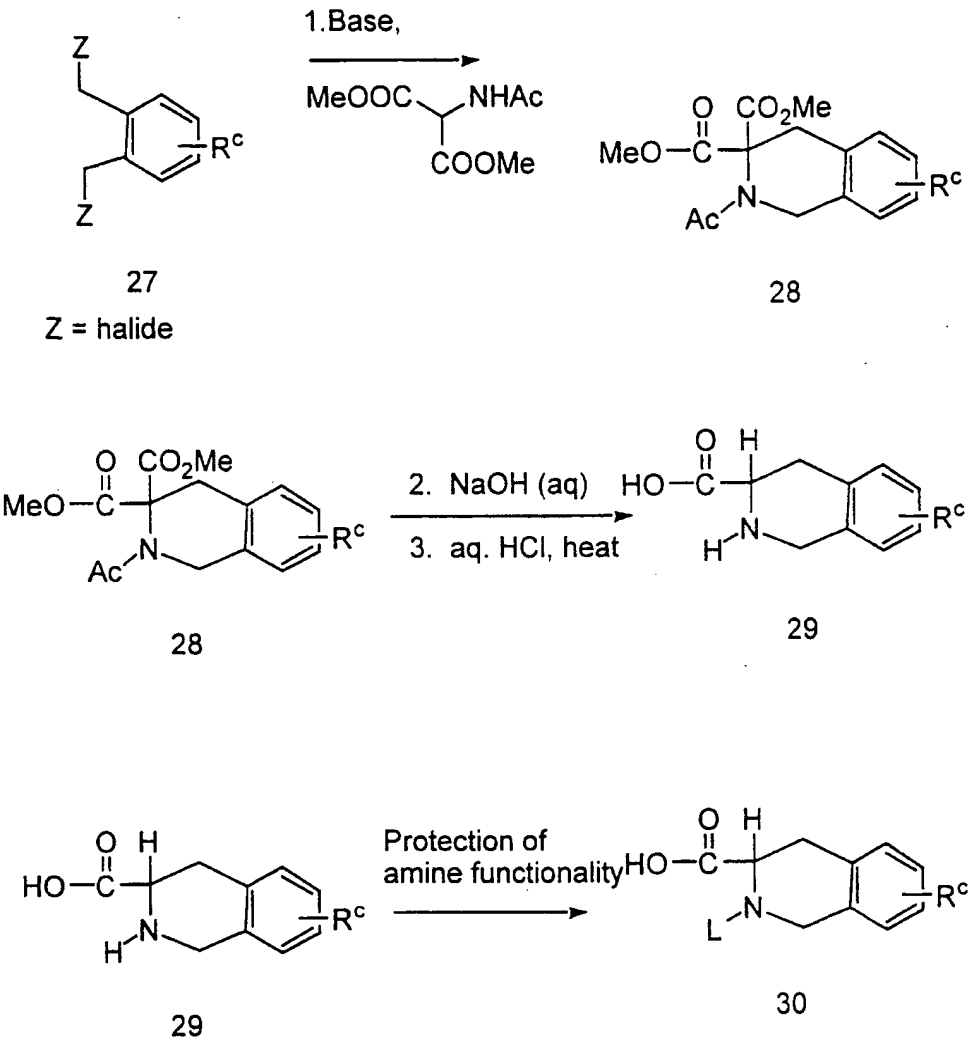
SCHEME 12



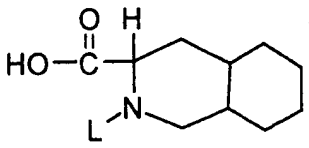
25 26

As shown in Scheme 12, a second method to prepare compounds of formula 5 includes alkylation of a dihalide (L = Br, Cl, I) of formula 27 with dimethylacetamidomalonate in the presence of a strong base such as NaH in DMF to afford alkylated material of formula 28. Treatment of esters of formula 28 with alkali leads to formation of the corresponding mono carboxylic acid which can be treated with refluxing hydrochloric to affect hydrolysis of the acetamide derivative to provide amino acid of formula 29. Once again, standard protection of the amino functionality provides intermediates of formula 30.

SCHEME 13



Saturated amino side chains of formula 31 can be prepared by hydrogenating compounds of formula 30 in the presence of rhodium or platinum catalysts.

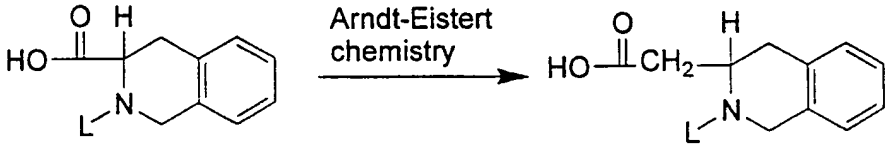


31

For example, following the method of Ornstein and coworkers (Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K.; Paschal, J. W. *J. Org. Chem.* **1991**, *56*, 4388), compound 30 can be hydrogenated in the presence of 5% Rh on alumina to give compound 31. Individual diastereomers of 31 can be resolved via classical resolution methods.

Schemes 14 illustrates one method for the preparation of tetrahydroisoquinolineacetic acid of formula 33. This is carried out conveniently by the Arndt-Eistert reaction which proceeds with retention of stereochemistry. Other methods involve require reduction of the acid or its ester derivative to an alcohol, conversion of the alcohol to a leaving group such as a mesylate or halide, displacement of it with cyanide anion and hydrolysis of the nitrile to the carboxylic acid by well documented literature methods.

SCHEME 14

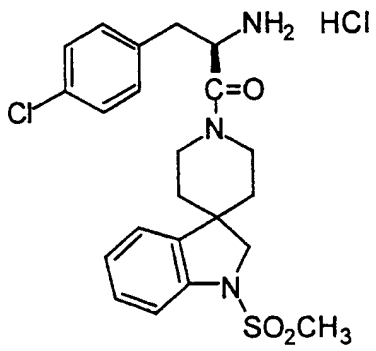


32 33

It is understood that in some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

Preparation of Intermediates

INTERMEDIATE 1



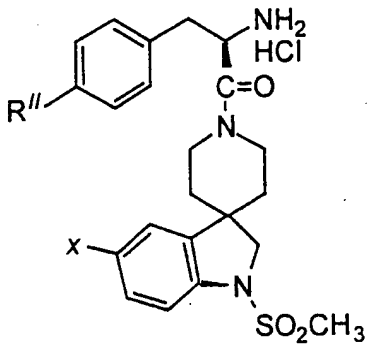
To a solution of N-Boc-D-4-chlorophenylalanine (10.95g; 36.55 mmol) in 166mL of dichloromethane was added 10.06g (33.27 mmol) of 1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'-piperidine] hydrochloride (see for example US Patent 5,536,716), 11mL of N-methylmorpholine, 7.01g of EDC and 4.94g of HOBt and stirred at room temperature for 18h. The reaction mixture was diluted with dichloromethane and washed with 1N HCl and saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over $MgSO_4$ and evaporated to give an intermediate that was chromatographed on silica gel using hexane-ethyl acetate (1:1) as the eluent to give the coupled product.

The product above was dissolved in 140 mL of dichloromethane and treated with 25 mL of 4.0M HCl in dioxane for 18h. The volatiles were removed and the sticky residue was dissolved in methanol and concentrated to dryness to provide the desired title compound.

^1H NMR (CD_3OD, 400MHz) 7.26-7.12 (m, 5 H); 4.90-4.37 (m, 1 H); 2.65-2.60 (m, 2 H); 1.97 (s, 3 H); 1.87 -1.82 (m, 1 H); 1.73-1.65 (m, 3 H).

INTERMEDIATE 2-5

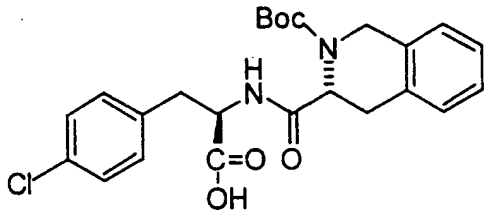
The following Intermediates were prepared from the appropriately substituted phenylalanine (Phe) and spiroindoline in an analogous manner to the one described for the preparation of Intermediate 1.



Intermediate	Phe	Rii	x
2	N-Boc-D-4-methoxy-Phe	CH_3O	H
3	N-Boc-D-4-bromo-Phe	Br	H
4	N-Boc-D-4-chloro-Phe	Cl	F*
5	N-Boc-D-4-methyl-Phe	CH3	H

*the starting material, 1,2-dihydro-5-fluoro-1-methanesulfonylspiro[3H-indole-3,4'-piperidine] hydrochloride, may be prepared according to general method disclosed in US Patent 5536716.

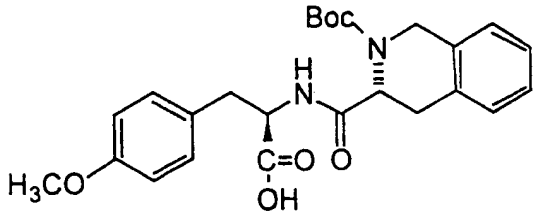
INTERMEDIATE 6



To a solution of of D-4-chlorophenylalanine methyl ester hydrochloride in dichloromethane was added N-Boc-D-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (N-Boc-D-Tic), EDC, HOBT and NMM, and the mixture was stirred at room temperature overnight. The crude product was isolated after standard work-up as described for the preparation of Intermediate 1. The crude ester was dissolved in methanol-water (1:1) and hydrolyzed to the desired acid by treatment with 2.5 eq. of NaOH. The reaction mixture was concentrated to ~50% of the volume, acidified to pH 2 with 1N HCl and extracted with dichloromethane. The combined organics were

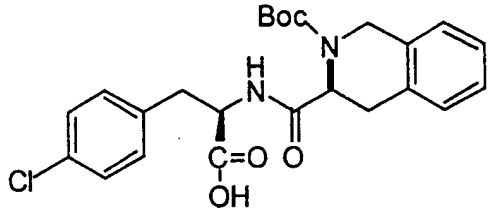
washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give the desired product as a colorless solid.

INTERMEDIATE 7



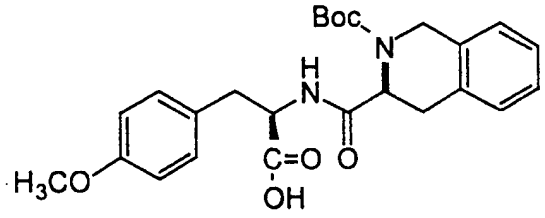
The title compound was synthesized in an analogous manner to Intermediate 3 using D-4-(methoxy)phenylalanine methyl ester hydrochloride in place of D-4-chlorophenylalanine methyl ester hydrochloride.

INTERMEDIATE 8



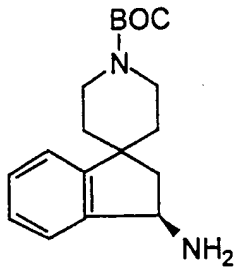
The title compound was synthesized in an analogous manner to Intermediate 3 using N-Boc-L-Tic in place of N-Boc-D-Tic.

INTERMEDIATE 9

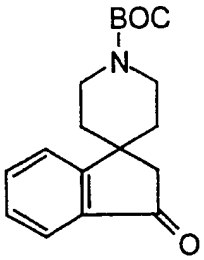


The title compound was synthesized in an analogous manner to Intermediate 4 using t N-Boc-L-Tic in place of N-Boc-D-Tic.

INTERMEDIATE 10. 3R-3-amino-1'-(t-butyloxycarbonyl)spiro[1H-indan-1,4'-piperidine]



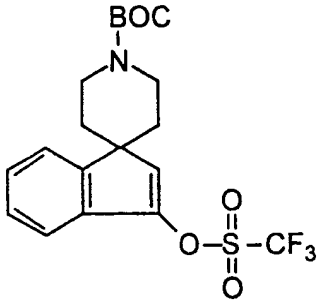
Step A: Preparation of 3-oxo-1'-(t-butyloxycarbonyl)spiro[1H-indan-1,4'-piperidine]



To a solution of 51.0 g (0.177 mol) of 1'-(t-butyloxy-carbonyl)spiro[1H-indene-1,4'-piperidine] [prepared by the method of Chambers, et al, J. Med. Chem., 1992, 35, 2036] in 200 ml of THF was added 430 ml (0.5 M in THF, 0.213 mol) of 9-BBN. The reaction mixture was heated at 70°C until TLC analysis indicated that the starting material was consumed (18 hrs). The solution was concentrated to ~300 ml and then cooled to 0°C and quenched with methanol (10 ml). 4 N Sodium hydroxide (213 ml) and 30 % hydrogen peroxide (108 ml) were added via an addition funnel over 45 minutes. The reaction mixture was stirred for 3.5 hours and then solid sodium sulfite was added until starch paper indicated that no more peroxides were present. The reaction mixture was extracted with ethyl acetate (4 X 1 vol). The ethyl acetate layer was dried over magnesium sulfate filtered and concentrated. The crude material was dissolved in dichloromethane (300 ml) and the solution was cooled to 0°C then celite (25 g) and PCC (57 g) were added in five

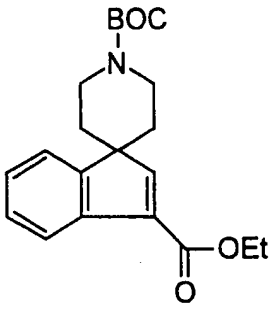
portions over 20 minutes. The reaction mixture was warmed to room temperature and stirred overnight. The solution was then diluted with ether and filtered through a pad of a mixture of celite and florisil. Purification by flash chromotgraphy (silica gel, hexane/ethyl acetate, 5:1 to 3:1) gave 58.6 g of the title compound. ^{1}H NMR (200 MHz, $CDCl_3$): 7.75-7.60 (m, 2H), 7.50-7.44 (m, 2H), 4.30-4.15 (m. 2H), 2.85 (dt, 2H), 2.63 (s, 2H), 1.98 (dt, 2H), 1.53-1.40 (m, 2H), 1.49 (s, 9H).

Step B: Preparation of 3-[(trifluoromethanesulfonyl)oxy]-1'-(t-butyloxycarbonyl)spiro[1H-indene-1,4'-piperidine]



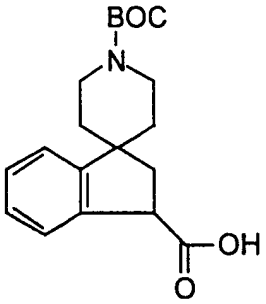
Potasium bis(trimethylsilyl)amide (127.5 ml, 0.5 M) was added to the ketone of Step A (16.0 g, 53 mmol) in THF (200 mL) at 0°C. The reaction mixture was stirred for one hour and then N-phenyltrifluromethanesulfonamide was added. The ice bath was allowed to melt and the reaction mixture was stirred overnight at room temperature. Water was added and the aqueous layer was extracted with ethyl acetate (3 X 1 vol). The organic layer was washed with brine and then dried over magnesium sulfate, filtered and then concentrated. The crude product was purified by flash chromatography (hexane/ethyl acetate 8 : 1) to give the title compound (17.8 g) as a waxy solid. ^{1}HNMR (200 MHz, $CDCl_3$): 7.65-7.14 (m, 4 H), 6.66 (s, 1 H), 4.30-4.15 (m, 2 H), 3.24-2.96 (m, 2H), 2.06 (dt, 2 H), 1.50 (s, 9 H), 1.49-1.38 (m, 2 H).

Step C: Preparation of 3-(ethoxycarbonyl)-1'-(t-butyloxycarbonyl)spiro[1H-indene-1,4'-piperidine]



A solution of 17.4 g of the intermediate from Step B, 11.0 ml of triethylamine, 634 mg of triphenylphosphine, and 240 mg of palladium acetate in 72 ml of ethanol and 158.0 ml of DMF was purged for 10 minutes with carbon monoxide and then stirred under a carbon monoxide atmosphere for 24 hours. The ethanol was removed in vacuum and the reaction mixture was diluted with water and extracted repeatedly with ethyl acetate. The ethyl acetate layer was washed with 1N HCl, water, and brine and then dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (hexane/ethyl acetate 8:1) provided 27.6 g of the title compound as a colorless oil. ^{1}HNMR (200 MHz, $CDCl_3$): 8.0-7.94 (m,1H), 7.7 (s, 1 H), 7.4-7.25 (m, 3H), 4.4 (q,2H), 4.25-4.15 (m, 2H), 3.13 (dt, 2H), 2.03 (dt, 2H), 1.5 (s, 9H), 1.55-1.35 (m, 2H), 1.4 (t, 3H).

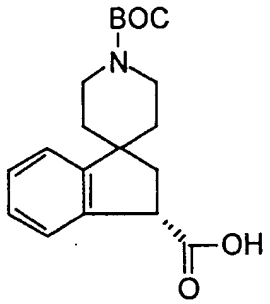
Step D: Preparation of 3-(carboxy)-1'-(t-butyloxycarbonyl)spiro[1H-indan-1,4'-piperidine]



To a suspension of Pd/C (1.7g) in ethanol (300 ml) was added the title compound (27 g) from Step C. The reaction mixture was purged with hydrogen and then shaken under a hydrogen atmosphere for 3 hours. The mixture was purged with

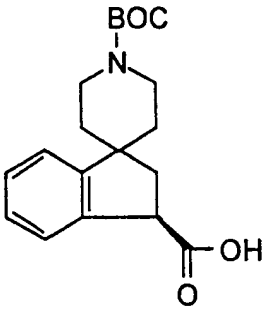
nitrogen and filtered through celite and concentrated to give the title compound (27 g). The crude product was dissolved in ethanol (200 ml) and 2N sodium hydroxide (76 ml) was added. The reaction mixture was heated to 50 ^{0}C for three hours then cooled and the ethanol was removed under vacuum and the residue was dissloved in ethyl acetate. 1N HCl was added and the layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 1 vol). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous sodium sulfate, filtered and concentrated to provide the title compound (23.8 g) as a white solid. ^{1}HNMR (200 MHz, $CDCl_3$): 7.50-7.42 (m, 1 H), 7.34-7.12 (m, 3 H), 4.22-4.04 (m, 3 H), 3.06-2.84 (m, 2 H), 2.40 (d, 2 H), 1.88-1.6 (m, 4 H), 1.50 (s, 9 H).

Step E: Preparation of 3S-3-(carboxy)-1'-(t-butyloxycarbonyl)spiro[1H-indan-1,4'-piperidine]



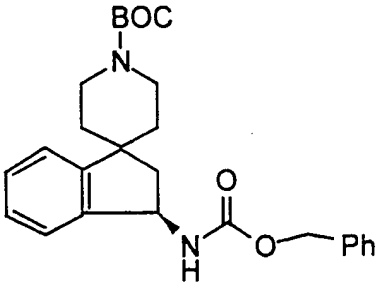
The acid from Step D (23.5 g, 0.07 mol) was dissolved in toluene (150 ml) and R- methylbenzylamine (9.02 ml) was added. The toluene solution was heated on a steam bath until everything was in solution. The solution was then seeded with crystals grown in the same way on a much smaller scale. The solution was allowed to sit overnight and then the mixture was filtered to give 15.8 g of crystals. The crystals were recrystalized from toluene two more times. The crystals (12 g) were dissolved in ethyl acetate /1 N HCl and the organic layer was washed with 1 N HCL (2 X 1 vol) and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated to give 8.9 g of the title compound. $[\alpha]^D$ = -16.9 (c= 0.84, methanol)

Step F: Preparation of 3R-3-(carboxy)-1'-(t-butyloxycarbonyl)spiro[1H-indan-1,4'-piperidine]



The mother liqueurs from Step E were washed with 1 N HCl (2 x1 vol) and brine dried over magnesium sulfate, filtered, and concentrated to give recovered acid (15.4 g). To this acid in toluene (100 mL) was added S-methylbenzylamine (5.95 mL). The crystals were recrystallized four times from toluene as above to give 12.3 g of salt. The salt was dissolved in ethyl acetate / 1 N HCl and washed with 1 N HCl (2 X 1 vol) and brine. The organic layer was dried over magnesium sulfate and filtered and concentrated to give the title compound (9.0 g). $[\alpha]^D = +17.1$ (c= 1.06, methanol).

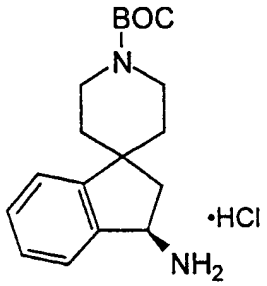
Step G: Preparation of 3R-3-[[(benzyloxy)carbonyl]amino]-1'-(t-butyloxycarbonyl)spiro[1H-indan-1,4'-piperidine]



To a stirred solution of 3R-3-(carboxy)-1'-(t-butyloxycarbonyl)spiro[1H-indan-1,4'-piperidine] (3.56 gm, 10.76 mmol) in dry toluene (30 mL) was added triethylamine (1.52 gm, 15.06 mmol), DPPA (3.55 gm, 12.91 mmol) and the mixture heated to 85°C for four hours to form 3R-3-(isocyanato)-1'-(t-butyloxycarbonyl)spiro[1H-indan-1,4'-piperidine]. The mixture was cooled to r.t. and benzyl alcohol (1.40 gm, 12.91 mmol) added and the reaction mixture stirred an additional 1.5 hr. The mixture was diluted with 50 ml of ethyl

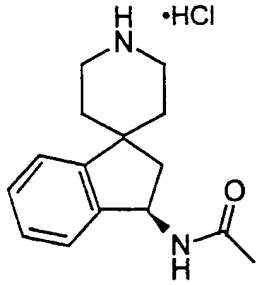
acetate and washed with 1 N HCl, brine and dried over $MgSO_4$. Concentrate and chromatograph (SiO_2, 1:1 EtOAc/hexane) to provide 4.1 grams of the clear, colorless viscous oil that is the title compound. ^{1}HNMR: ($CDCl_3$; 300 Mhz). ESI-MS calc. for C26H32N2O4: 436; Found 454 ($M+H+NH_3$).

Step H: Preparation of 3R-3-amino-1'-(t-butyloxycarbonyl)spiro[1H-indan-1,4'-piperidine] hydrochloride salt



To a stirred solution of the product of Step G (4.1 gm, 9.4 mmol) in methanol (50 mL) was added $HCl_{(conc.)}$ (0.9 mL, 10.3 mmol) and $Pd(OH)_2$-C (0.5 gm). The mixture was stirred vigorously under an H_2 atomosphere for 16 hr. The reaction mixture was filtered through celite and the solvent removed *in vacuo* to provide 2.85 gm of the white solid. ESI-MS calc. for C18H26N2O2: 302; Found 303 (M+H), 203 (M+H-Boc).

INTERMEDIATE 11. 3R-3-(acetylamino)-spiro[1H-indan-1,4'-piperidine] HCl

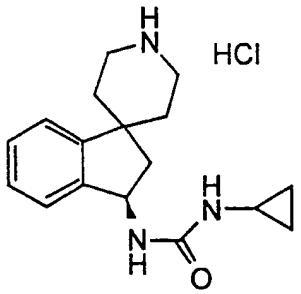


To a stirred solution of Intermediate 10 (1.5 gm, 4.4 mmol) and DMAP (54 mg, 0.4 mmol) in dry dichloromethane (15 mL) was added triethylamine (1.3 gm, 13.3 mmol), acetic anhydride (0.68 gm, 6.6 mmol) and the mixture stirred for 16 hr. The reaction mixture was concentrated, diluted with 50 ml of ethyl acetate and

washed with $NaHCO_3$ (sat'd), brine and dried over $MgSO_4$. The organic phase was oncentrated and chromatographed (SiO_2, 3:1:0.1 EtOAc/hexane/methanol) to provide 1.6 grams (81%) of the N-Boc protected title compound as white solid. ESI-MS calc. for C20H28N2O3: 344; Found 345 (M+H).

To a stirred solution of N-Boc protected title compound (1.2 g, 3.6 mmol) in methanol (1.0 mL), HCl-EtOAc was added to the mixture (5 mL). The reaction was stirred for 20 minutes and the solvent was removed in vacuo to afford 0.95 g of the product. ESI-MS calc. for C15H20N2O: 244; Found 245 (M+H), 286 (M+H+CH3CN).

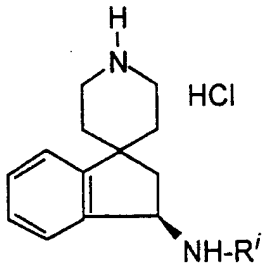
INTERMEDIATE 12



The general procedure described in Step G of Intermediate 10 was followed using cyclopropylamine instead of benzyl alchol to react with the isocyanato compound to provide the N-Boc protected title compound. The N-Boc protecting group was removed according to the general procedure described in Intermediate 11 to provide the title compound.

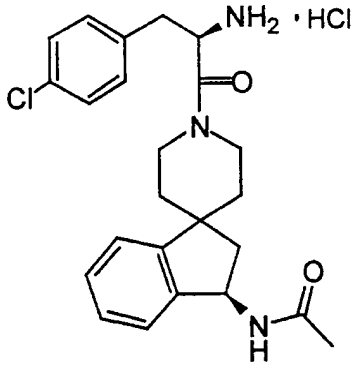
INTERMEDIATES 13-24

Following the general procedure described for Intermediate 11, and using Intermediate 10 and the appropriate acylating agent, or following the general procedure described for Intermediate 12 using the appropriate amine to react with the isocyanato compound described in Intermediate 10, step G, Intermediates 13-24 were prepared.



Intermediate	Acylating Agent/Amine	R^i
13	methanesulfonyl chloride	SO_2CH_3
14	3-pyridinecarbonyl chloride	CO-3-pyridyl
15	4-pyridinecarbonyl chloride	CO-4-pyridyl
16	2-pyrazinecarbonyl chloride	CO-2-pyrazinyl
17	2-aminopyrimidine	CONH-2-pyrimidinyl
18	piperidine	$CO\text{-}N(CH_2)_5$
19	morpholine	$CO\text{-}N(CH_2)_2O(CH_2)_2$
20	2-aminothiazole	CONH-2-thiazolyl
21	2-pyridinecarbonyl chloride	CO-2-pyridyl
22	benzoyl chloride	CO-Ph
23	benzenesulfonyl chloride	SO_2Ph
24	2-thiophenecarboxylic acid	CO-2-thienyl

5 INTERMEDIATE 25



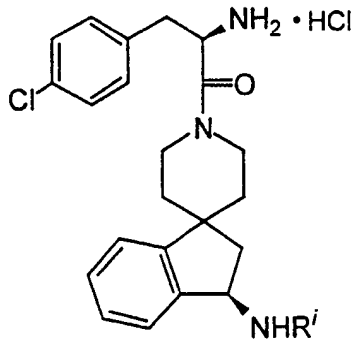
To a stirred solution of Intermediate 11 (657 mg, 2.34 mmol), N-Boc-D-4-chlorophenylalanine (737 mg, 2.5 mmol), PyBrop (1091 mg, 2.34 mmol) and

DMAP (172 mg, 1.4 mmol) in dichloromethane, 6 mL was added DIEA (907 mg, 7.02 mmol). The solution was stirred 16 hr, concentrated and chromatographed directly (SiO_2,19:1 EtOAc/ methanol) to provide 1.08 gm of the N-Boc protected title compound as white solid. ESI-MS calc. for C29H36ClN3O4: 525; Found 526 (M+H), 426 (M+H-Boc).

To a stirred solution of the N-Boc protected title compound from the previous step (1.1 g, 2.1 mmol) in methanol (0.5 mL), HCl-EtOAc was added (5 mL). The reaction was stirred for 20 minutes and the solvent was removed *in vacuo* to afford 0.95 g of the title compound. ESI-MS calc. for C24H28ClN3O2: 425; Found 426 (M+H), 443 (M+H+NH_3).

INTERMEDIATE 26-38

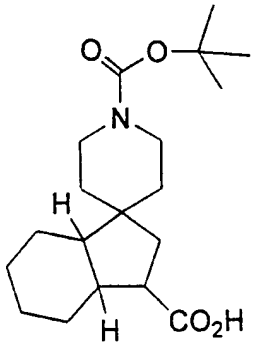
Following the procedure described for Intermediate 25 and unsing Intermediates 12-24, the following compounds were prepared:



Intermediate	R^i
26	CONH-cyclopropyl
27	SO_2CH_3
28	CO-3-pyridyl
29	CO-4-pyridyl
30	CO-2-pyrazinyl
31	CONH-2-pyrimidinyl
32	CO-N$(CH_2)_5$
33	CO-N$(CH_2)_2O(CH_2)_2$
34	CONH-2-thiazolyl
35	CO-2-pyridyl

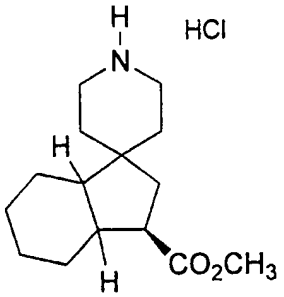
36	CO-Ph
37	SO_2Ph
38	CO-2-thienyl

INTERMEDIATE 39



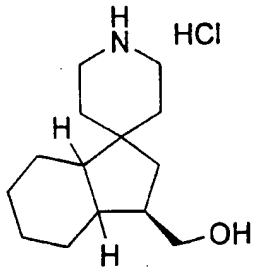
A heterogeneous mixture of the product of Intermediate 10, Step F (5.0 gm, 15.1 mmol), Rh/Al_2O_3 (0.85 gm) in ethanol (50 mL) was agitated under an atmosphere of hydrogen (2000 psi, 100°C) for 18 hr. The mixture was filtered through celite and the solvent removed *in vacuo* to provide (3.85 gm) (75 %) of the white solid which is the title compound. ESI-MS calc. for:; Found (M+H).

INTERMEDIATE 40



To a stirred solution of HCl-MeOH (mL) was added Intermediate 39 (350 mg, 104 mmol) and the mixture stirred 16 hr. The solvent was removed *in vacuo* to provide (300 mg) (100 %) of the white solid which is the title compound. ESI-MS calc. For C15H26ClNO2: 287; Found 288(M+H).

INTERMEDIATE 41



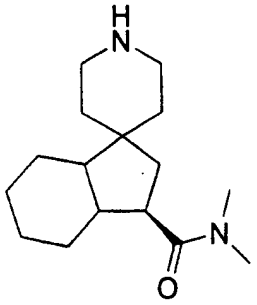
Step A.

In a dry three-necked round-bottomed flask equipped with magnetic stir bar and nitrogen purge, was added Intermediate 39 (2.5 gm, 7.41 mmol) and tetrahydrofuran (7.5 mL, anhydrous). The mixture was stirred and cooled to –10°C and borane –dimethylsulfide (7.4 mL, 2M in THF, 2 eq.) was added dropwise over a period of 20 min. When the addition was complete, the mixture was warmed to r.t., refluxed for one hour, and cooled to r.t. The reaction was quenched with the addition of 1 mL water/acetic acid accompanied by vigorous stirring. The mixture was concentrated under reduced pressure, diluted with ethyl acetate, washed with saturated NaHCO3, brine and then dried over MgSO4. The solvent was removed in vacuo to provide (2.32 gm) (97%) of the white solid which is the N-Boc protected title compound. ESI-MS calc. For C19H33NO3: 323; Found 324(M+H).

Step B.

To a stirred mixture of N-Boc protected title compound (180 mg, 0.4 mmol.) in a minimal amount of methanol (ca. 100 μL) was added 5 mL of a saturated HCl-EtOAc solution. The mixture was stirred 20 min and the solvent removed in vacuo to provide (154 mg) of the white solid which is the title compound. ESI-MS calc. For C14H26ClNO: 260; Found 261(M+H).

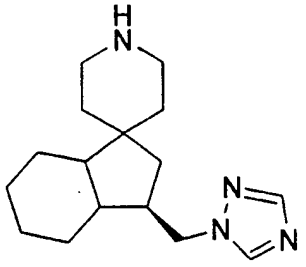
INTERMEDIATE 42



To a stirred solution of Intermediate 39 (400 mg, 1.2 mmol), PyBrop (607 mg, 1.2 mmol) and DMAP (92 mg, 0.7 mmol) in dichloromethane, 2.0 mL was added DIEA (459 mg, 3.6 mmol). The reaction mixture was stirred 16 hr, diluted with dichloromethane, washed with 1N HCl and concentrated in vacuo. The residue was purified via preparative HPLC to provide 435 mg of the white solid that is the N-Boc protected title compound. ESI-MS calc. For C21H36N2O3: 364; Found 365(M+H).

The procedure described in Step B of Intermediate 41 was followed using the N-Boc protected title compound to provide the title compound. ESI-MS 265 (M+H).

INTERMEDIATE 43

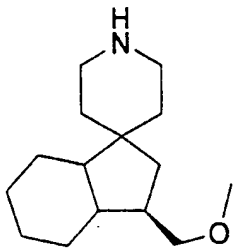


To a solution of intermediate 41 (1.8 gm, 5.6 mmol) in dichloromethane (15 mL) add triethylamine (1.69 gm, 3.0 eq) stir and cool to 0°C, then add mesyl chloride (1.0 gm, 1.5 eq) and continue stirring three hours. Concentrate, dilute with DMF (6 mL), stir and add sodium triazole (1.0 gm, 3 eq.). dilute with ethyl acetate then wash with saturated NaHCO3, brine and dry over MgSO4. Remove solvent in vacuo to provide

(154 mg) of the yellow solid which is the N-Boc protected title compound. ESI-MS calc. For C21H32N4O3: 388; Found 389(M+H).

The procedure described in Step B of Intermediate 41 was followed using the N-Boc protected title compound to provide the title compound. ESI-MS 289 (M+H).

INTERMEDIATE 44

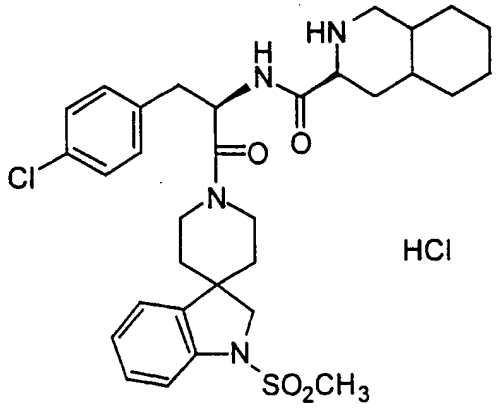


To a solution of intermediate 41 (0.5 gm, 1.5 mmol) in tetrahydrofuran (5 mL) was added imidazole (105 mg, 1.0 eq), and the mixture was stirred and cooled to 0°C, then sodium hydride (74 mg, 2.0 eq) was added thereto and stirring continued for 30 min. Methyl iodide (439 mg, 2 eq.) was added via syringe, and the mixture was warmed to r.t. and stirring was contined for 2 hr. The reaction mixture was concentrated and partitioned between EtOAc / 1N HCl, washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to provide (250 mg) of the yellow oil which is the title N-protected title compound. ESI-MS calc. For C20H35NO3: 337; Found 338(M+H).

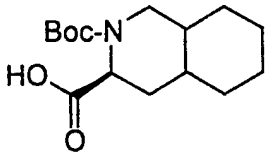
The procedure described in Step B of Intermediate 41 was followed using the N-Boc protected title compound to provide the title compound. ESI-MS 238 (M+H).

The following Examples are provided to illustrate the invention, and are not to be construed as limiting the scope of the invention in any manner.

EXAMPLE 1



Step A: Preparation of 3S-N-Boc-3-decahydroisoquinolinecarboxylic acid



A 50-mL, three-necked, round-bottomed flask equipped with an nitrogen inlet adapter, glass stopper, and rubber septum was charged with commercially available *N*-Boc-(*L*)-Tic (1.00 g, 3.6 mmol) and 18 mL of DMF. Potassium carbonate (0.597 g, 4.30 mmol) was then added followed by the addition of methyl iodide (1.1 mL, 18.0 mmol) via syringe. The resulting mixture was stirred at room temperature for 20 h and then methylene chloride and water were added. The aqueous layer was separated and extracted with two portions of methylene chloride, and the combined organic phases were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (1:1 ethyl acetate-hexane) to give *N*-Boc-(*L*)-Tic methyl ester (1.17 g) as a yellow oil.

A solution of *N*-Boc-(*L*)-Tic methyl ester (1.05 g, 3.60 mmol) and 12 mL of methanol was charged with 5% rhodium on alumina (0.53 g) and then heated at 55-60 °C under 40 psi of hydrogen for 36 h. After cooling to room temperature, the

reaction mixture was filtered through Celite using methanol to rinse and concentrated. The crude oil was then filtered again through Celite using ethyl acetate as the eluent and concentrated to give methyl 3*S*-*N*-Boc-3-decahydroisoquinoline-carboxylate (0.733 g) as a clear oil. ESI-MS calcd for $C_{16}H_{27}NO_4$: 297: Found: 298 (m + 1). Hydrogenation of a similar compound gave exclusively the *cis*-ring junction products as a mixture of diastereomers, see: Ornstein, P. L.; Arnold, M. B.; Augenstein, N. K.; Paschal, J. W. *J. Org. Chem.* **1991**, *56*, 4388.

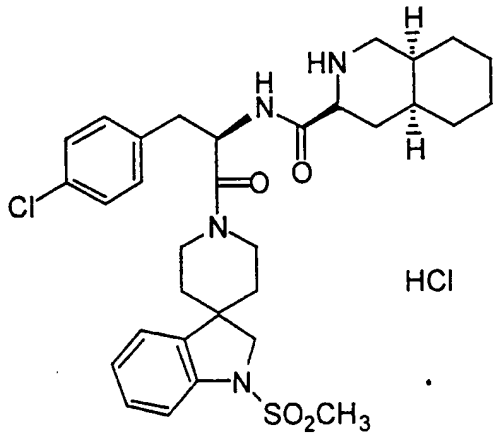
A 25-mL, round-bottomed flask was charged with methyl 3*S*-*N*-Boc-3-decahydro-isoquinolinecarboxylate (0.733 g, 2.46 mmol) and 7 mL of methanol. An aqueous 1 N NaOH solution (5 mL) was then added and the resulting mixture was stirred at room temperature for 22 h. The mixture was then concentrated and the resulting residue was dissolved in water and cooled at 0 ° C in an ice-water bath. The pH was then adjusted using a 1 N HCl to pH 4, and the cloudy mixture was diluted with ethyl acetate. The aqueous layer was separated and extracted with two portions of ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated to give 3*S*-*N*-Boc-3-decahydro-isoquinolinecarboxylic acid (0.667 g) as a very thick yellow oil. The ^{1}H NMR spectrum shows the presence of two diastereomers; *cis*-ring junction isomers from the previous hydrogenation reaction.

Step B: Preparation of title compound

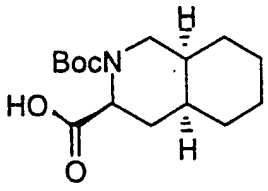
A 25-mL, round-bottomed flask was charged with Intermediate 1 (0.102 g, 0.182 mmol) and then a solution of the acid of Step A (0.057 g, 0.201 mmol) in 1.2 mL of methylene chloride was added. The mixture was cooled at 0 ° C in an ice-water bath and then NMM (0.10 mL, 0.910 mmol), HOBt • H_2O (0.027 g, 0.201 mmol), and EDC • HCl (0.039 g, 0.201 mmol) were added. The resulting mixture was stirred at room temperature for 22 h, and was then diluted with methylene chloride and washed with two portions of 1 N HCl solution, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (9:1 methylene chloride:acetone) to give the N-Boc protected title compound (0.096 g) as a white solid. ESI-MS calcd for $C_{37}H_{49}N_4SO_6Cl$: 712: Found: 713 (m + 1). The ^{1}H NMR spectrum shows the presence of two *cis*-ring junction diastereomers from the hydrogenation reaction.

A 25-mL, round-bottomed flask was charged with the N-Boc protected title compound (0.080 g, 0.112 mmol) and 0.3 mL of methylene chloride. Trifluoroacetic acid (0.3 mL) was then added and the mixture was stirred at room temperature for 65 min. The mixture was diluted with toluene and concentrated, and the resulting oil was diluted with toluene again and concentrated. The residue was dissolved in ethyl acetate and washed with 1 N NaOH solution, and the combined organic phases were dried over potassium carbonate, filtered, and concentrated to give a clear oil. The free amine was then dissolved in 0.5 mL of ethyl acetate and 0.13 mL of a 1 N HCl solution in ether was added dropwise via syringe. The mixture was diluted with ether and the precipitate was then filtered under nitrogen to give the title compound (0.056 g) as a white powder. ESI-MS calcd for $C_{32}H_{41}N_4SO_4Cl$: 612: Found: 613 (m + 1).

EXAMPLE 2



Step A: Preparation of [3*S*(3α,4aβ,8aβ)]-*N*-Boc-decahydro-3-isoquinolinecarboxylic acid



A 25-mL, round-bottomed flask equipped with a reflux condenser was charged with commercially available [3*S*(3α,4aβ,8aβ)]-*N*-*tert*-butyldecahydro-3-isoquinolinecarboxamide (1.0 g, 4.19 mmol) and 10 mL of aqueous 6 N HCl solution. The solution was heated at 80 °C for 23 h and then cooled to 0 °C and diluted with 12 mL of 5 N NaOH solution (pH = 13). The aqueous solution was extracted with ethyl acetate and then transferred to a 100-mL, round-bottomed flask and diluted with 25 mL of dioxane. Di-*tert*-butyl dicarbonate (1.0 g, 4.61 mmol) was then added and the mixture was stirred at room temperature for 23.5 h while occasionally adjusting the pH using 5 N NaOH solution (pH = 10). The resulting mixture was diluted with ethyl acetate and water and the layers were separated. The aqueous layer was cooled at 0 °C in an ice-water bath and then 1 N HCl solution was added portionwise until pH = 2. The aqueous layer was extracted with three portions of ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated to give [3*S*(3α,4aβ,8aβ)]-*N*-Boc-decahydro-3-isoquinolinecarboxylic acid (0.427 g) as a white solid.

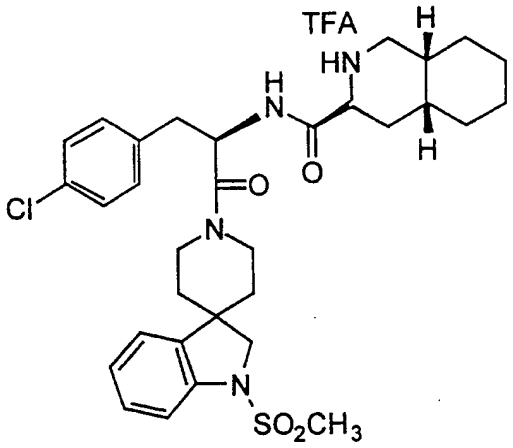
Step B: Preparation of Title Compound

A 25-mL, round-bottomed flask was charged with Intermediate 1 TFA salt (prepared as Intermediate 1 except TFA is used in place of HCl, 0.123 g, 0.219 mmol) and 1.3 mL of methylene chloride and then the mixture was cooled at 0 ° C in an ice-water bath. Acid from Step A (0.068 g, 0.241 mmol), NMM (0.10 mL, 0.910 mmol), HOBt • H_2O (0.033 g, 0.241 mmol), and EDC • HCl (0.046 g, 0.241 mmol) were added. The resulting mixture was stirred at room temperature for 22 h, and was then diluted with methylene chloride and washed with two portions of 1 N HCl solution, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (9:1 methylene chloride:acetone) to give N-Boc protected title compound (0.112 g) as a white solid. ESI-MS calcd for $C_{37}H_{49}N_4SO_6Cl$: 712: Found: 713 (m + 1).

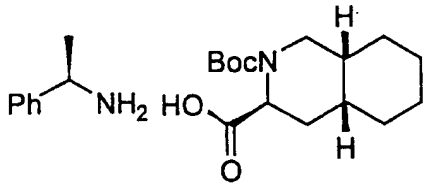
A 25-mL, round-bottomed flask was charged with the N-Boc protected title compound (0.110 g, 0.154 mmol) and 0.4 mL of methylene chloride. Trifluoroacetic acid (0.4 mL) was then added and the mixture was stirred at room temperature for 45 min. The mixture was diluted with toluene and concentrated, and the resulting oil was diluted with toluene again and concentrated. The residue was

dissolved in ethyl acetate and washed with 1 N NaOH solution (back-extracted with two portions of ethyl acetate), and the combined organic phases were dried over potassium carbonate, filtered, and concentrated to give a yellow oil. The free amine was then dissolved in 0.5 mL of ethyl acetate and 0.18 mL of a 1 N HCl solution in ether was added dropwise via syringe. The mixture was diluted with ether and the precipitate was then filtered under nitrogen to give the title compound (0.072 g) as a white powder. ESI-MS calcd for $C_{32}H_{41}N_4SO_4Cl$: 612: Found: 613 (m + 1).

EXAMPLE 3



STEP A: Preparation of [3*S*(3α,4aα,8aα)]-*N*-Boc-decahydro-3-isoquinolinecarboxylic acid, (R)- α-methylbenzylamine salt



A 25-mL, round-bottomed flask was charged with acid 3S-N-Boc-3-decahydroisoquinolinecarboxylic acid from Example 1 (0.453 g, 1.60 mmol) and 14 mL of ethyl acetate. (R)-α-methylbenzyl amine (0.21 mL, 1.60 mmol) was then added and the resulting mixture sat at room temperature under nitrogen for 24 h. The

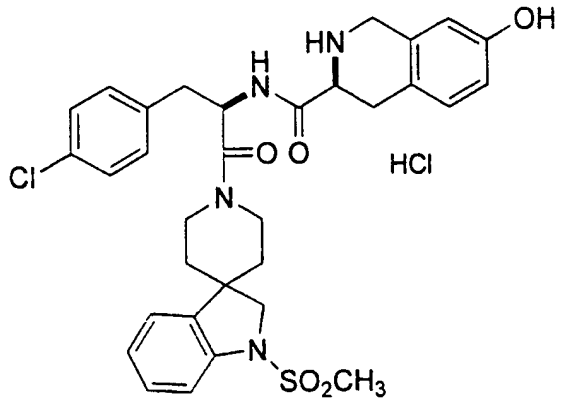
precipitate was then filtered to give 0.393 g of a white powder. The white powder was then recrystallized (ethyl acetate-ethanol) to give [3*S*(3α,4aα,8aα)]-*N*-Boc-decahydro-3-isoquinolinecarboxylic acid, (R)- α-methylbenzylamine salt (0.130 g) as a white solid.

STEP B: Preparation of Title Compound

A 15-mL, round-bottomed flask was charged with the free acid of the product of Step A (obtained by washing intermediate from STEP A with 10% aqueous citric acid) (0.020 g 0.049 mmol) and 0.3 mL of methylene chloride. Intermediate 1 (0.022 g, 0.045 mmol), NMM (0.020 mL, 0.180 mmol), HOBt • H_2O (0.007 g, 0.049 mmol), and EDC • HCl (0.009 g, 0.047 mmol) were added. The resulting mixture was stirred at room temperature for 17 h, and was then diluted with methylene chloride and washed with two portions of 1 N HCl solution, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (1:1 ethyl acetate-hexane) to give N-Boc protected title compound (0.023 g) as a white solid.

A 10-mL, round-bottomed flask was charged with the N-Boc protected title compound (0.022 g, 0.031 mmol) and 0.2 mL of methylene chloride. Trifluoroacetic acid (0.2 mL) was then added and the mixture was stirred at room temperature for 1 h. The mixture was diluted with toluene and concentrated twice, and then the oil was diluted with ether and concentrated to afford the title compound (0.021 g) as a white solid. ESI-MS calcd for $C_{32}H_{41}N_4SO_4Cl$: 612: Found: 613 (m + 1).

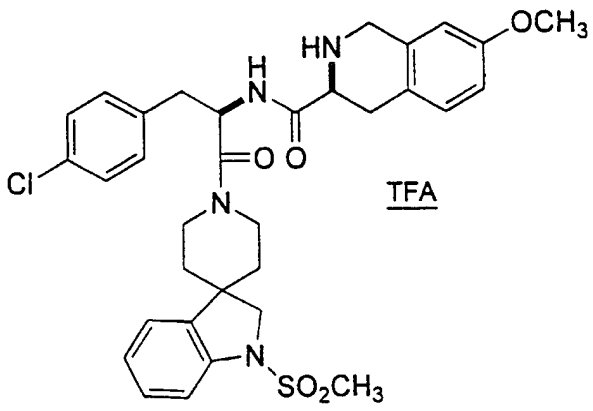
EXAMPLE 4



To a solution of Intermediate 1 (450.1 mg, 1.01 mmol) in methylene chloride (10 mL) was added N-Boc-7-hydroxy-L-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (7-OH-N-Boc-L-Tic, 355.5 mg, 1.21 mmol), HOBt (164.1 mg, 1.21 mmol), EDC (232.3 mg, 1.21 mmol), and NMM (0.5 mL, 4.55 mmol). The mixture was stirred at room temperature overnight and then quenched with EtOAc (50 mL). The organic solution was washed with 5 % aq HCl solution (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), and dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by MPLC (4:1 DCM:aceton) to give the N-Boc protected title compound as a white solid (558.8 mg, 76.6%). ESI-MS calc. for $C_{37}H_{43}ClN_4O_7S$ 722; Found 723 (M+1).

To a solution of N-Boc protected title compound (79.5 mg, 109.9 μmol) and anisole (0.1 mL) in DCM (1.0 mL) was added TFA (0.5 mL). The mixture was stirred at room temperature until no starting material left (TLC). The solvents were removed under reduced pressure and diethyl ether was added to give a white solid (TFA salt). The salt was added to an aquoues solution of 1 N NaOH (15 mL) and extracted with ethyl acetate (2x15 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was dissolved in ethyl acetate (0.5 mL) to which was added 1N HCl in diethyl ether to yield the title compound as a white solid (53.6 mg, 73.9%, HCl salt). ESI-MS calc. for $C_{32}H_{35}ClN_4O_5S$ 622; Found 623 (M+1).

EXAMPLE 5

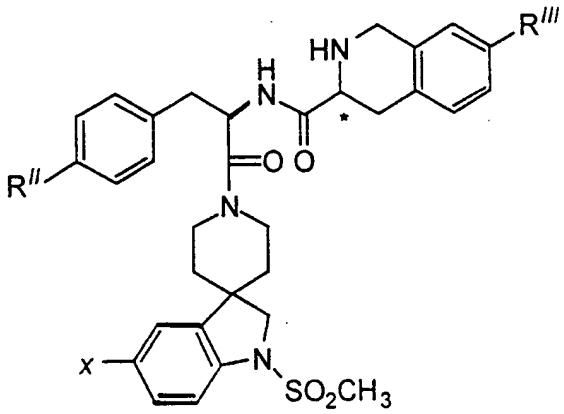


To a mixture of the N-Boc protected compound of Example 4 (153.4 mg, 212.1 μmol) and K_2CO_3 (58.8 mg, 425.5 μmol) in DMF (5.0 mL) was added methyl iodide (20.0 μL, 321.4 μmol). The mixture was stirred at room temperature overnight and then quenched with 1N HCl (aquoues, 50 mL), and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the N-Boc protected title compound as a colorless oil (147.0 mg, 94.0%). ESI-MS calc. for $C_{38}H_{45}ClN_4O_7S$ 736; Found 737 (M+1).

To a solution of the N-Boc protected title compound (179.9 mg, 244.0 μmol) and anisole (0.1 mL) in DCM (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at room temperature until no starting material left (TLC). The solvents were removed under reduced pressure and diethyl ether was added to provids the title compound as a white solid (143.2 mg, 78.1%). ESI-MS calc. for $C_{33}H_{37}ClN_4O_5S$ 636; Found 637 (M+1).

EXAMPLES 6-15

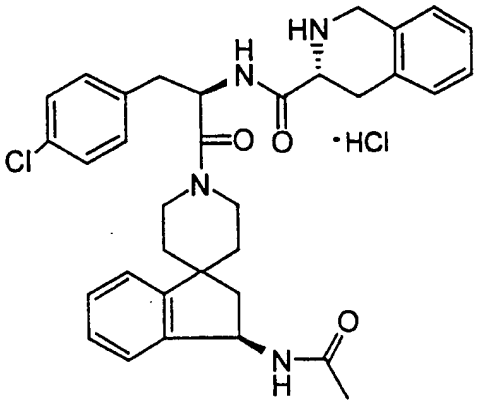
The general procedure described in Example 4 was followed to provide compounds of Examples 6-15 using the Intermediates and acids listed below:



Stereoconfiguration same as the Tic starting material

Ex.	Interm.	Acid	Salt	R^{ii}	R^{iii}	x	EI-MS
6	3	N-Boc-D-Tic	TFA	Br	H	H	651 (M+1) 653 (M+3)
7	3	N-Boc-L-Tic	TFA	Br	H	H	651 (M+1) 653 (M+3)
8	4	7-OH-N-Boc-L-Tic	TFA	Cl	OH	F	641 (M+1)
9	3	7-OH-N-Boc-D-Tic	TFA	Br	OH	H	667 (M+1) 669 (M+3)
10	3	7-OH-N-Boc-L-Tic	TFA	Br	OH	H	667 (M+1) 669 (M+3)
11	1	7-OH-N-Boc-D-Tic	TFA	Cl	OH	H	623 (M+1)
12	5	N-Boc-L-Tic	TFA	CH_3	H	H	587 (M+1)
13	1	N-Boc-D-Tic	HCl	Cl	H	H	653 (M+H)
14	2	N-Boc-D-Tic	HCl	CH_3O	H	H	
15	2	N-Boc-L-Tic	HCl	CH_3O	H	H	

EXAMPLE 16

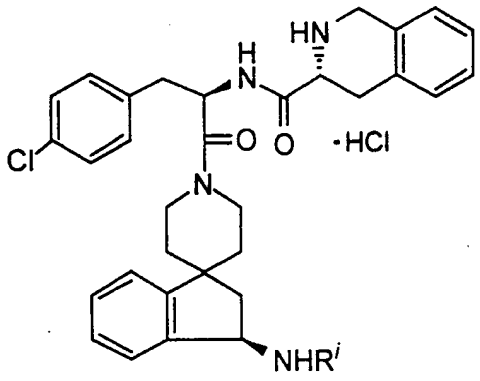


To a stirred solution of Intermediate 25 (150 mg, 0.35 mmol), N-Boc-D-Tic (162 mg, 0.35 mmol), PyBrop (164 mg, 0.35 mmol) and DMAP (172 mg, 1.4 mmol) in dichloromethane, 6 mL was added DIEA (26 mg, 0.21 mmol). The solution was stirred 16 hr, concentrated and chromatographed directly (SiO_2,19:1 EtOAc/ methanol) to provide 200 mg of the N-Boc protected title compound as a white solid. ESI-MS calc. for C39H45ClN4O5: 684; Found 685 (M+H), 585 (M+H-Boc).

To a stirred solution of the N-Boc protected title compound from the previous step (160m g, 0.23 mmol) in methanol (0.25 mL), HCl-EtOAc was added (5 mL). The reaction was stirred for 20 minutes and the solvent was removed *in vacuo* to afford 138mg of the title compound as a white solid. ESI-MS calc. for C34 H37 N4 O3 Cl1: 584; Found 585 (M+H), 607 (M+H+NH_3).

EXAMPLES 17-29

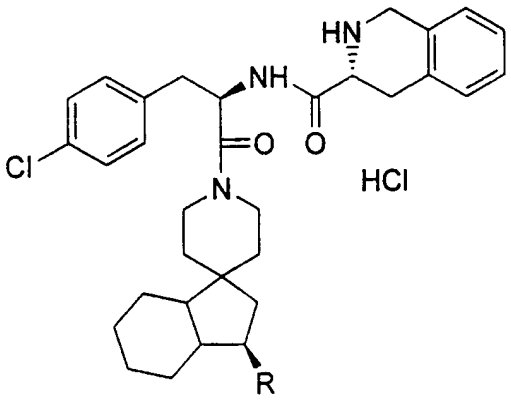
The general procedure described in Example 13 was followed using Intermedates 26-38 to synthesize the following compounds:



Example	Intermediate	R^i	EI-MS
17	26	CONH-cyclopropyl	
18	27	SO_2CH_3	
19	28	CO-3-pyridyl	
20	29	CO-4-pyridyl	
21	30	CO-2-pyrazinyl	649 (M+H)
22	31	CONH-2-pyrimidinyl	664 (M+H)
23	32	CO-N$(CH_2)_5$	654 (M+H)
24	33	CO-N$(CH_2)_2O(CH_2)_2$	656 (M+H)
25	34	CONH-2-thiazolyl	669 (M+H)
26	35	CO-2-pyridyl	648 (M+H)
27	36	CO-Ph	647 (M+H)
28	37	SO_2Ph	683 (M+H)
29	38	CO-2-thienyl	653 (M+H)

EXAMPLE 30-34

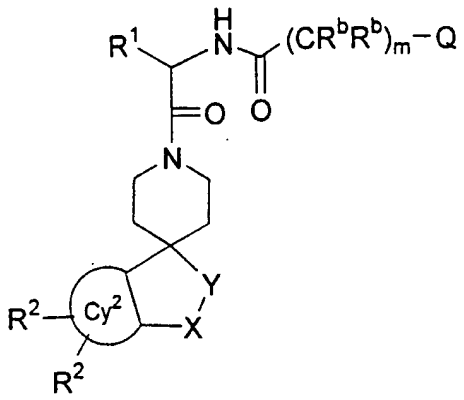
Following the general procedures described for Intermediate 25 and Example 16 and starting with Intermediates 40-44, the following compounds were prepared:



Example	Intermediate	R	ESI-MS
30	40	CO_2CH_3	592 (M+H)
31	42	$C(O)N(CH_3)_2$	603 (M+H)
32	43	CH_2-1,2,4-triazol-1-yl	615 (M+H)
33	41	CH_2OH	564 (M+H)
34	44	CH_2OCH_3	578 (M+H)

WHAT IS CLAIMED IS:

1. A compound having the formula I:

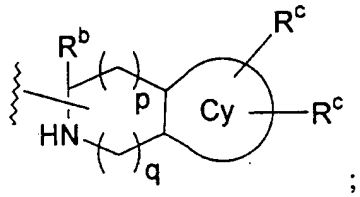


I

wherein

Cy^2 is a six-membered aromatic ring containing 0 or 1 N atom or cyclohexane;

Q is



;

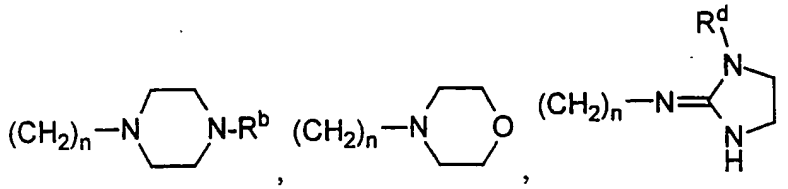
X is O, CH_2, SO_2, $CHCO_2R^b$, $CHSO_2R^a$, $CHC(O)N(R^b)_2$, NR^b, NSO_2R^a, $NSO_2N(R^b)_2$, $NCOR^a$, $NCON(R^b)_2$, $CHN(R^b)COR^a$, $CHN(R^b)SO_2R^a$, $CHCH_2OR^b$, or $CH(CH_2)$-heteroaryl;

Y is $(CH_2)_r$, CH-C_{1-8}alkyl, O, C=O or SO_2, with the proviso that when Y is O, the ring atom of X is carbon;

R^1 is H, C_{1-8}alkyl, $CH(R^b)$-aryl, $CH(R^b)$-heteroaryl, $(CH_2)_n$-C_{5-6}cycloalkyl in which aryl and heteroaryl are optionally substituted by one or two R^c groups;

R^2 is H or halo;

R^a is R^b, $(CH_2)_nN(R^b)_2$, $(CH_2)_nN(R^b)C(=NR^d)NR^b$, $(CH_2)_nNH$-2-pyridyl, $(CH_2)_nNH$-2-imidazolyl, $(CH_2)_nNH$-2-thiazolyl, $(CH_2)_nNH$-2-pyrimidinyl,



;

R^b is H, C_{1-8}alkyl, $(CH_2)_n$aryl, $(CH_2)_n$heteroaryl, C_{3-6}cycloalkyl; or 2 R^b together with the nitrogen atom to which they are attached form a 5- or 6-membered ring optionally containing an additional heteroatom selected from O, S, and NR^1;

R^c is R^b, halo, OR^b, $NHSO_2R^b$, $N(R^b)_2$, CN, NO_2, $SO_2N(R^b)_2$, SO_2R^b, CF_3, OCF_3; or two R^c groups attached to adjacent carbon atoms together form methylenedioxy;

R^d is H, NO_2, or CN;

Cy is aryl, 5- or 6-membered heteroaryl, 5- or 6-membered heterocyclyl, or 5-or 6-membered carbocyclyl;

n is 0 to 3;

m, p and q are independently 0, 1 or 2;

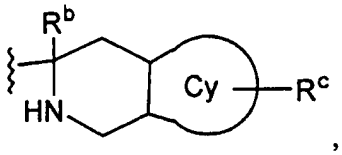
r is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein Cy^2 is benzene or cyclohexane.

3. A compound of Claim 1 wherein X is $CHCO_2R^b$, $CHC(O)N(R^b)_2$, NSO_2R^a, $CHN(R^b)COR^a$, $CHN(R^b)SO_2R^a$, $CHCH_2OR^b$ or $CHCH_2$-heteroaryl.

4. A compound of Claim 1 wherein Q is

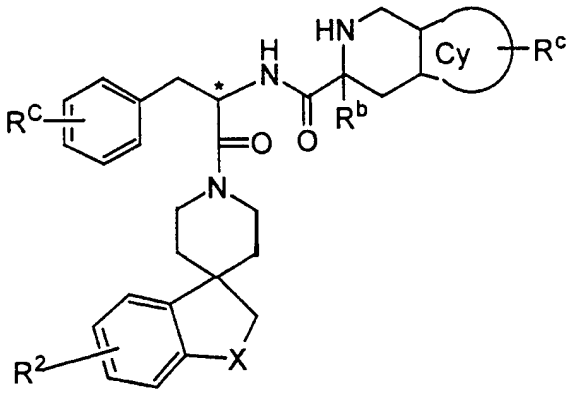


,

R^b and R^c are as defined in Claim 1, and Cy is aryl, 5- or 6-membered heteroaryl, or 5-or 6-membered carbocyclyl.

5. A compound of Claim 1 wherein R^1 is CH_2-aryl in which aryl is optionally substituted by R^c.

6. A compound of Claim 1 having the formula Ia:

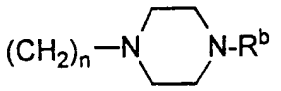
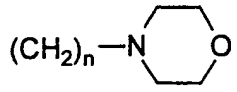


Ia

wherein

X is $CHCO_2R^b$, $CHC(O)N(R^b)_2$, NSO_2R^a, $CHN(R^b)COR^a$, or $CHN(R^b)SO_2R^a$;

R^2 is H or halo;

R^a is R^b, $(CH_2)_nN(R^b)_2$, $(CH_2)_n$NH-2-pyridyl, $(CH_2)_n$NH-2-imidazolyl, $(CH_2)_n$NH-2-thiazolyl, $(CH_2)_n$NH-2-pyrimidinyl,  , or  ;

R^b is H, $C_{1\text{-}8}$alkyl, $(CH_2)_n$aryl, $(CH_2)_n$heteroaryl, or $C_{3\text{-}6}$cycloalkyl;

R^c is H, halo, R^b, OR^b, CF_3, OCF_3;

Cy is benzene, pyridine, imidazole or cyclohexane;

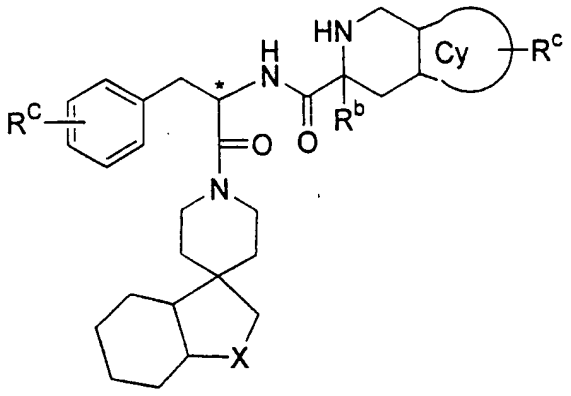
n is 0 to 3;

or a pharmaceutically acceptable salt thereof.

7. A compound of Claim 6 wherein the carbon atom marked with * has the *R* configuration.

8. A compound of Claim 7 wherein Cy is benzene or cyclohexane.

10. A compound of Claim 1 having the formula Ib:



Ib

wherein

X is $CHCO_2R^b$, $CHC(O)N(R^b)_2$, $CHCH_2OR^b$ or $CHCH_2$-heteroaryl;

R^b is H, C_{1-8}alkyl, $(CH_2)_n$aryl, $(CH_2)_n$heteroaryl, or C_{3-6}cycloalkyl;

R^c is H, halo, R^b, OR^b, CF_3, OCF_3;

Cy is benzene, pyridine, imidazole or cyclohexane;

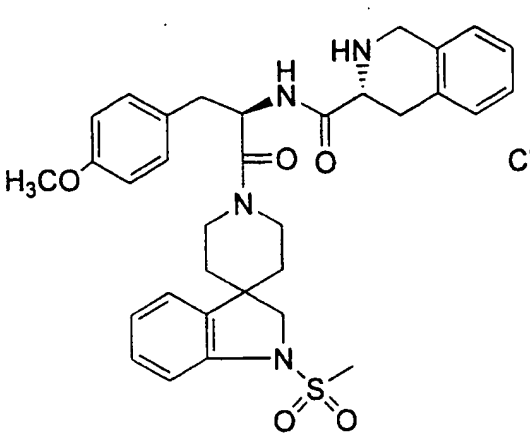
n is 0 to 3;

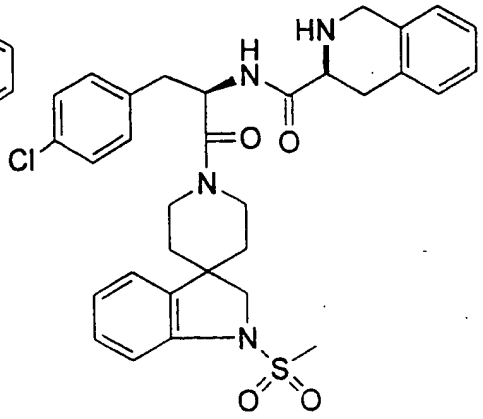
or a pharmaceutically acceptable salt thereof.

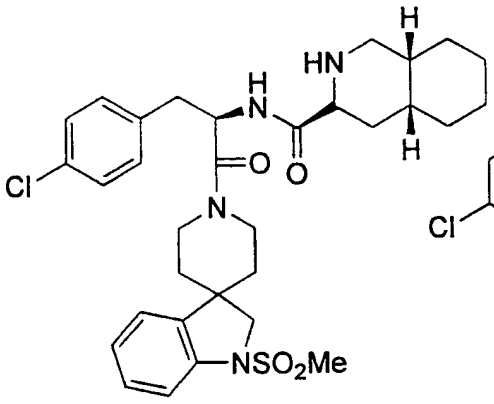
11. A compound of Claim 10 wherein the carbon atom marked with * has the *R* configuration.

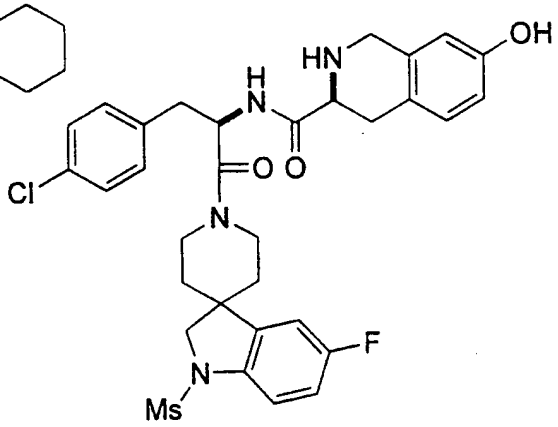
12. A compound of Claim 11 wherein Cy is benzene or cyclohexane.

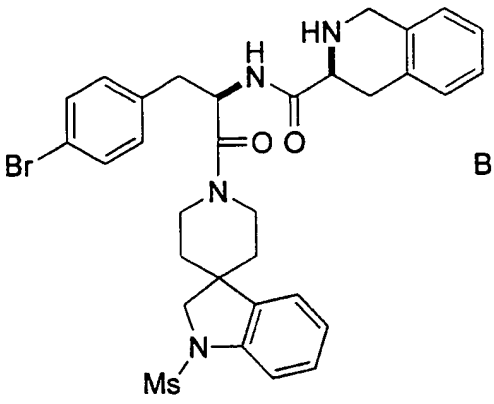
13. A compound selected from the group consisting of :

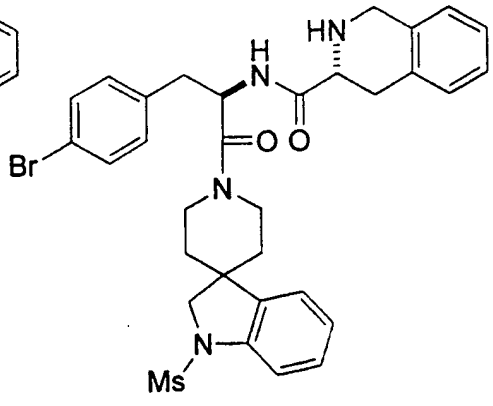


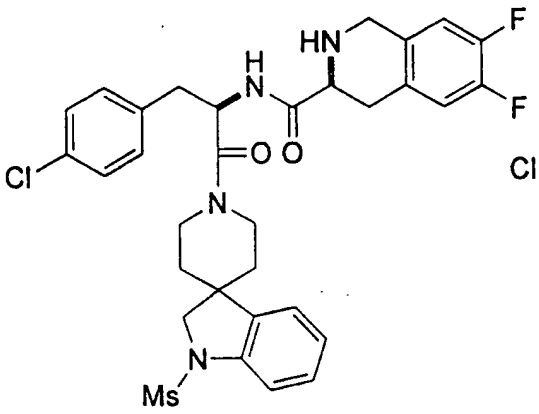


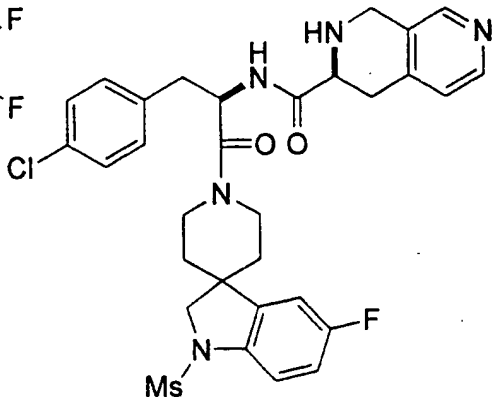


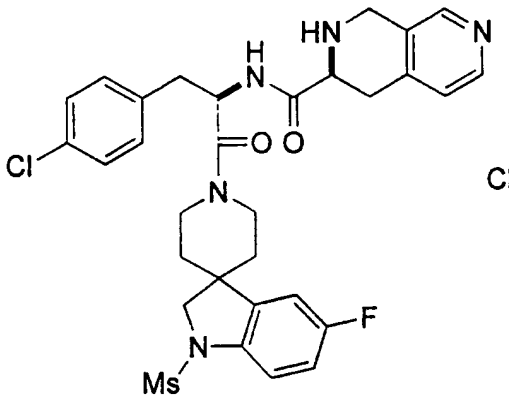


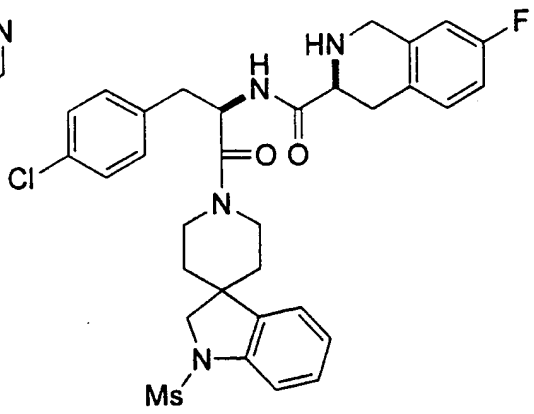












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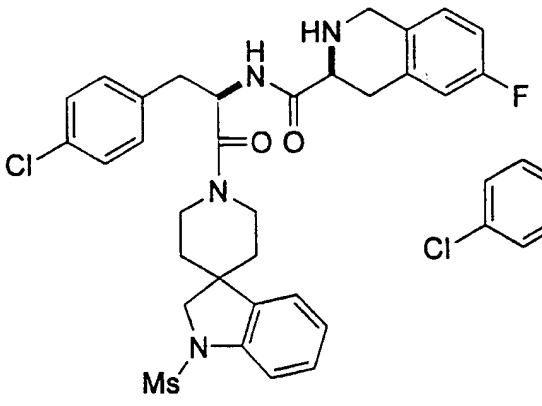

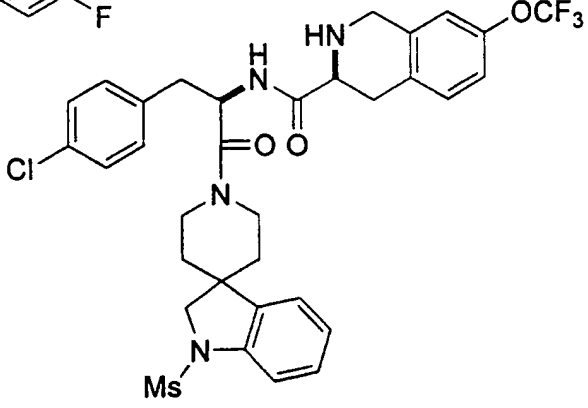

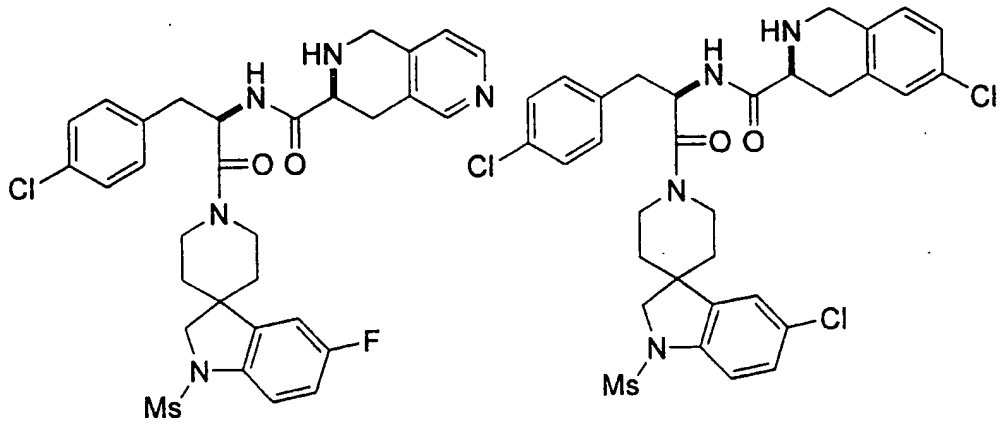

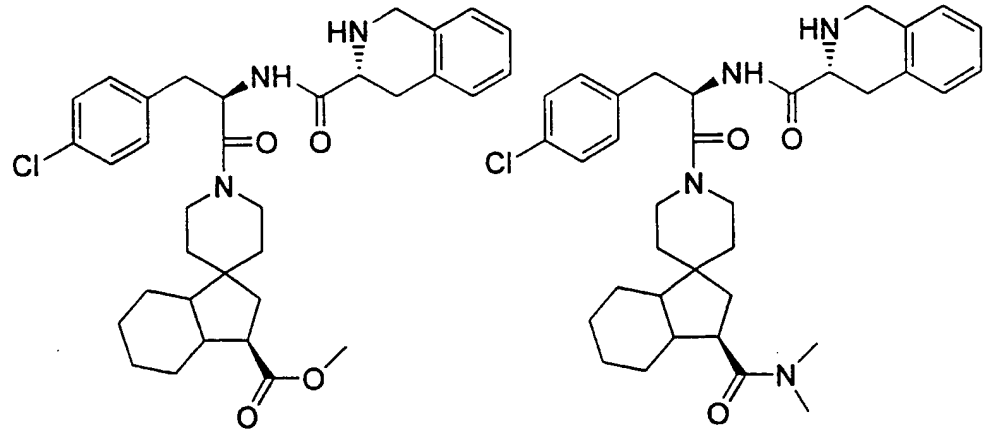

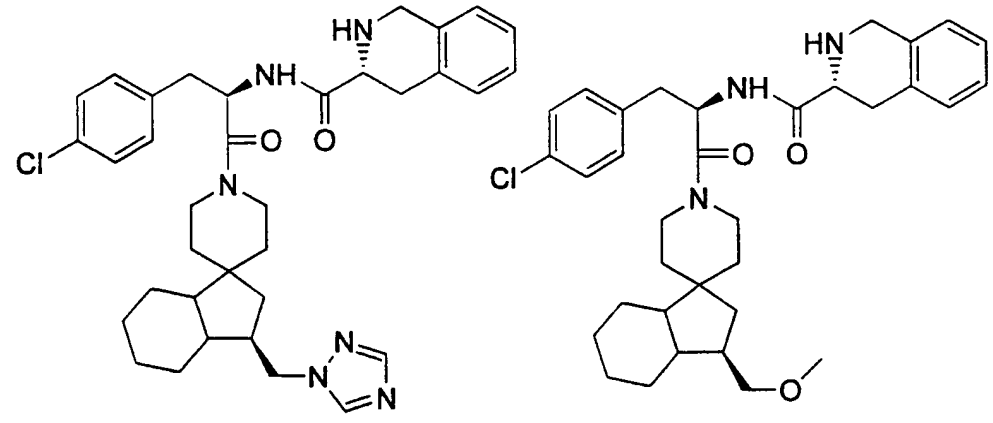

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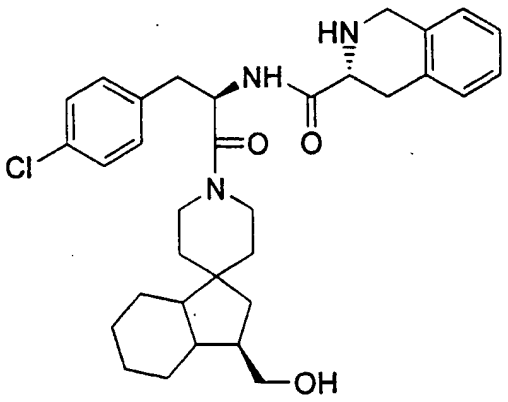

14. A method for the treatment or prevention of disorders, diseases or conditions responsive to the activation of melanocortin receptor which comprises administering to a mammal in need of such treatment or prevention an effective amount of a compound of Claim 1.

15. A method for the treatment or prevention of obesity which comprises administering to a mammal in need of such treatment or prevention an effective amount of a compound of Claim 1.

16. A method for the treatment or prevention of diabetes mellitus which comprises administering to a mammal in need of such treatment or prevention an effective amount of a compound of Claim 1.

17. A method for the treatment or prevention of male or female sexual dysfunction which comprises administering to a mammal in need of such treatment or prevention an effective amount of a compound of Claim 1.

18. A method for the treatment or prevention of erectile dysfunction which comprises administering to a mammal in need of such treatment or prevention an effective amount of a compound of Claim 1.

19. A method for the treatment or prevention of male or female sexual dysfunction which comprises administering to a mammal in need of such treatment or prevention an effective amount of an agonist of melanocortin-4 receptor.

20. A method for the treatment or prevention of erectile dysfunction which comprises administering to a mammal in need of such treatment or prevention an effective amount of an agonist of melanocortin-4 receptor.

21. A method for the treatment or prevention of female sexual dysfunction which comprises administering to a mammal in need of such treatment or prevention an effective amount of an agonist of melanocortin-4 receptor.

22. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

23. A pharmaceutical composition of Claim 22 further comprising a second active ingredient selected from an insulin sensitizer, insulin mimetic, sulfonylurea, α-glucosidase inhibitor, HMG-CoA reductase inhibitor, sequestrant cholesterol lowering agent, β3 adrenergic receptor agonists, neuropeptide Y antagonist, phosphodiester V inhibitor, and α-2 adrenergic receptor antagonist.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/13252

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/47, 31/445; C07D 217/26, 401/12, 471/04
US CL :514/278; 546/17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/278; 546/17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,578,593 A (CHEN et al.) 26 November 1996, columns 2-8; column 71, example 31.	1-22
A	US 5,731,408 A (HADLEY et al.) 24 March 1998, columns 1-2.	1-22
A	WO 96/05203 A1 (MERCK SHARP & DOHME LTD.) 22 February 1996, see entire doucument, especially examples 52-54.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 01 SEPTEMBER 1999	Date of mailing of the international search report 26 OCT 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EVELYN HUANG Telephone No. (703) 308-1235

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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BAKSHI, Raman, Kumar** [IN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **NARGUND, Ravi, P.** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). **YE, Zhixiong** [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/91752 A1

(54) Title: MELANOCORTIN RECEPTOR AGONISTS

(57) Abstract: Certain novel compounds and derivatives thereof are agonists of the human melanocortin receptor(s) and, in particular, are selective agonists of the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of MC-4R, such as obesity, diabetes, sexual dysfunction, including erectile dysfunction and female sexual dysfunction.

TITLE OF THE INVENTION
MELANOCORTIN RECEPTOR AGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present invention is related to U.S. provisional application Serial No. 60/207,918, filed May 30, 2000, the contents of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to novel compounds and derivatives thereof, their synthesis, and their use as melanocortin receptor (MC-R) agonists. More particularly, the compounds of the present invention are selective agonists of the melanocortin-4 receptor (MC-4R) and are thereby useful for the treatment of disorders responsive to the activation of MC-4R, such as obesity, diabetes, and male and/or female sexual dysfunction.

BACKGROUND OF THE INVENTION

Pro-opiomelanocortin (POMC) derived peptides are known to affect food intake. Several lines of evidence support the notion that the G-protein coupled receptors (GPCRs) of the melanocortin receptor (MC-R) family, several of which are expressed in the brain, are the targets of POMC derived peptides involved in the control of food intake and metabolism. A specific single MC-R that may be targeted for the control of obesity has not yet been identified, although evidence has been presented that MC-4R signalling is important in mediating feed behavior (S.Q. Giraudo et al., "Feeding effects of hypothalamic injection of melanocortin-4 receptor ligands," Brain Research, 80: 302-306 (1998)).

Evidence for the involvement of MC-R's in obesity includes: i) the agouti (A^{vy}) mouse which ectopically expresses an antagonist of the MC-1R, MC-3R and MC-4R is obese, indicating that blocking the action of these three MC-R's can lead to hyperphagia and metabolic disorders; ii) MC-4R knockout mice (D. Huszar et al., Cell, 88: 131-141 (1997)) recapitulate the phenotype of the agouti mouse and these mice are obese; iii) the cyclic heptapeptide MT-II (a non-selective MC-1R, -3R, -4R, and -5R agonist) injected intracerebroventricularly (ICV) in rodents, reduces food intake in several animal feeding models (NPY, *ob/ob*, agouti, fasted) while ICV injected SHU-9119 (MC-3R and -4R antagonist; MC-1R and -5R agonist) reverses

this effect and can induce hyperphagia; and iv) chronic intraperitoneal treatment of Zucker fatty rats with an α-NDP-MSH derivative (HP228) has been reported to activate MC-1R, -3R, -4R, and -5R and to attenuate food intake and body weight gain over a 12-week period (I. Corcos et al., "HP228 is a potent agonist of melanocortin receptor-4 and significantly attenuates obesity and diabetes in Zucker fatty rats," Society for Neuroscience Abstracts, 23: 673 (1997)).

Five distinct MC-R's have thus far been identified, and these are expressed in different tissues. MC-1R was initially characterized by dominant gain of function mutations at the Extension locus, affecting coat color by controlling phaeomelanin to eumelanin conversion through control of tyrosinase. MC-1R is mainly expressed in melanocytes. MC-2R is expressed in the adrenal gland and represents the ACTH receptor. MC-3R is expressed in the brain, gut, and placenta and may be involved in the control of food intake and thermogenesis. MC-4R is uniquely expressed in the brain, and its inactivation was shown to cause obesity (A. Kask, et al., "Selective antagonist for the melanocortin-4 receptor (HS014) increases food intake in free-feeding rats," Biochem. Biophys. Res. Commun., 245: 90-93 (1998)). MC-5R is expressed in many tissues, including white fat, placenta and exocrine glands. A low level of expression is also observed in the brain. MC-5R knockout mice reveal reduced sebaceous gland lipid production (Chen et al., Cell, 91: 789-798 (1997)).

Erectile dysfunction denotes the medical condition of inability to achieve penile erection sufficient for successful sexual intercourse. The term "impotence" is oftentimes employed to describe this prevalent condition. Approximately 140 million men worldwide, and, according to a National Institutes of Health study, about 30 million American men suffer from impotency or erectile dysfunction. It has been estimated that the latter number could rise to 47 million men by the year 2000. Erectile dysfunction can arise from either organic or psychogenic causes, with about 20% of such cases being purely psychogenic in origin. Erectile dysfunction increases from 40% at age 40, to 67% at age 75, with over 75% occurring in men over the age of 50. In spite of the frequent occurrence of this condition, only a small number of patients have received treatment because existing treatment alternatives, such as injection therapies, penile prosthesis implantation, and vacuum pumps, have been uniformly disagreeable [for a discussion, see "ABC of sexual health - erectile dysfunction," Brit. Med. J. 318: 387-390 (1999)]. Only more recently have more viable treatment modalities become available, in particular orally active

agents, such as sildenafil citrate, marketed by Pfizer under the brand name of Viagra®. Sildenafil is a selective inhibitor of type V phosphodiesterase (PDE-V), a cyclic-GMP-specific phosphodiesterase isozyme [see R.B. Moreland et al., "Sildenafil: A Novel Inhibitor of Phosphodiesterase Type 5 in Human Corpus Cavernosum Smooth Muscle Cells," Life Sci., 62: 309-318 (1998)]. Prior to the introduction of Viagra on the market, less than 10% of patients suffering from erectile dysfunction received treatment. Sildenafil is also being evaluated in the clinic for the treatment of female sexual dysfunction.

The regulatory approval of Viagra® for the oral treatment of erectile dysfunction has invigorated efforts to discover even more effective methods to treat erectile dysfunction. Several additional selective PDE-V inhibitors are in clinical trials. UK-114542 is a sildenafil backup from Pfizer with supposedly improved properties. IC-351 (ICOS Corp.) is claimed to have greater selectivity for PDE-V over PDE-VI than sildenafil. Other PDE-V inhibitors include M-54033 and M-54018 from Mochida Pharmaceutical Co. and E-4010 from Eisai Co., Ltd.

Other pharmacological approaches to the treatment of erectile dysfunction have been described [see, e.g., "Latest Findings on the Diagnosis and Treatment of Erectile Dysfunction," Drug News & Perspectives, 9: 572-575 (1996); "Oral Pharmacotherapy in Erectile Dysfunction," Current Opinion in Urology, 7: 349-353 (1997)]. A product under clinical development by Zonagen is an oral formulation of the alpha-adrenoceptor antagonist phentolamine mesylate under the brand name of Vasomax®. Vasomax® is also being evaluated for the treatment of female sexual dysfunction.

Drugs to treat erectile dysfunction act either peripherally or centrally. They are also classified according to whether they "initiate" a sexual response or "facilitate" a sexual response to prior stimulation [for a discussion, see "A Therapeutic Taxonomy of Treatments for Erectile Dysfunction: An Evolutionary Imperative," Int. J. Impotence Res., 9: 115-121 (1997)]. While sildenafil and phentolamine act peripherally and are considered to be "enhancers" or "facilitators" of the sexual response to erotic stimulation, sildenafil appears to be efficacious in both mild organic and psychogenic erectile dysfunction. Sildenafil has an onset of action of 30-60 minutes after an oral dose with the effect lasting about 4 hours, whereas phentolamine requires 5-30 minutes for onset with a duration of 2 hours. Although sildenafil is effective in a majority of patients, it takes a relatively long time for the compound to show the desired effects. The faster-acting phentolamine appears to be

less effective and to have a shorter duration of action than sildenafil. Oral sildenafil is effective in about 70% of men who take it, whereas an adequate response with phentolamine is observed in only 35-40% of patients. Both compounds require erotic stimulation for efficacy. Since sildenafil indirectly increases blood flow in the systemic circulation by enhancing the smooth muscle relaxation effects of nitric oxide, it is contraindicated for patients with unstable heart conditions or cardiovascular disease, in particular patients taking nitrates, such as nitroglycerin, to treat angina. Other adverse effects associated with the clinical use of sildenafil include headache, flushing, dyspepsia, and "abnormal vision," the latter the result of inhibition of the type VI phosphodiesterase isozyme (PDE-VI), a cyclic-GMP-specific phosphodiesterase that is concentrated in the retina. "Abnormal vision" is defined as a mild and transient "bluish" tinge to vision, but also an increased sensitivity to light or blurred vision.

Synthetic melanocortin receptor agonists (melanotropic peptides) have been found to initiate erections in men with psychogenic erectile dysfunction [See H. Wessells et al., "Synthetic Melanotropic Peptide Initiates Erections in Men With Psychogenic Erectile Dysfunction: Double-Blind, Placebo Controlled Crossover Study," J. Urol., 160: 389-393 (1998); Fifteenth American Peptide Symposium, June 14-19, 1997 (Nashville TN)]. Activation of melanocortin receptors of the brain appears to cause normal stimulation of sexual arousal. In the above study, the centrally acting α-melanocyte-stimulating hormone analog, melanotan-II (MT-II), exhibited a 75% response rate, similar to results obtained with apomorphine, when injected intramuscularly or subcutaneously to males with psychogenic erectile dysfunction. MT-II is a synthetic cyclic heptapeptide, Ac-Nle-c[Asp-His-DPhe-Arg-Trp-Lys]-NH_2, which contains the 4-10 melanocortin receptor binding region common to α-MSH and adrenocorticotropin, but with a lactam bridge. It is a non-selective MC-1R, -3R, -4R, and –5R agonist (Dorr et al., Life Sciences, Vol. 58, 1777-1784, 1996). MT-II (also referred to as PT-14) (Erectide®) is presently in clinical development by Palatin Technologies, Inc. and TheraTech, Inc. as a non-penile subcutaneous injection formulation. It is considered to be an "initiator" of the sexual response. The time to onset of erection with this drug is relatively short (10-20 minutes) with a duration of action approximately 2.5 hours. Adverse reactions observed with MT-II include nausea, flushing, loss of appetite, stretching, and yawning and may be the result of activation of MC-1R, MC-2R, MC-3R, and/or MC-5R. MT-II must be administered parenterally, such as by subcutaneous, intravenous,

or intramuscular route, since it is not absorbed into the systemic circulation when given by the oral route. Compositions of melanotropic peptides and methods for the treatment of psychogenic erectile dysfunction are disclosed in U.S. Patent No. 5,576,290, assigned to Competitive Technologies.

Because of the unresolved deficiencies of the various pharmacological agents discussed above, there is a continuing need in the medical arts for improved compounds, methods and compositions to treat individuals suffering from psychogenic and/or organic erectile dysfunction. Such compounds and methods should have wider applicability, enhanced convenience and ease of compliance, short onset of action, reasonably long duration of action, and minimal side effects with few contraindications, as compared to agents now available.

It is therefore an object of the present invention to provide compounds which are useful as melanocortin receptor agonists.

It is another object of the present invention to provide compounds which are selective agonists of the melanocortin-4 (MC-4R) receptor.

It is another object of the present invention to provide pharmaceutical compositions comprising melanocortin receptor agonists.

It is another object of the present invention to provide methods for the treatment or prevention of disorders, diseases, or conditions responsive to the activation of the melanocortin receptor in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

It is another object of the present invention to provide compounds and pharmaceutical compositions useful for the treatment or prevention of obesity, diabetes mellitus, and male and/or female sexual dysfunction.

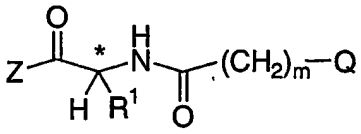
It is another object of the present invention to provide compounds and pharmaceutical compositions for the treatment or prevention of erectile dysfunction.

It is another object of the present invention to provide methods for the treatment or prevention of obesity, diabetes mellitus, and male and/or female sexual dysfunction.

These and other objects will become readily apparent from the detailed description that follows.

SUMMARY OF THE INVENTION

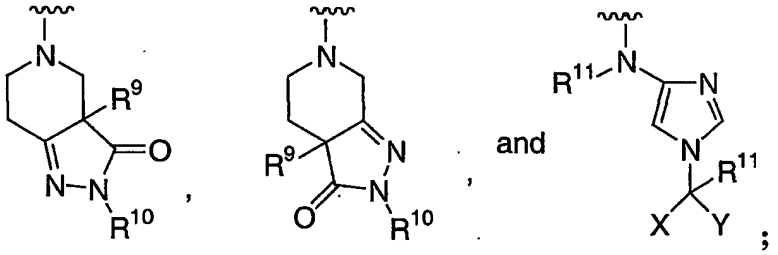
The present invention relates to novel compounds of structural formula I:



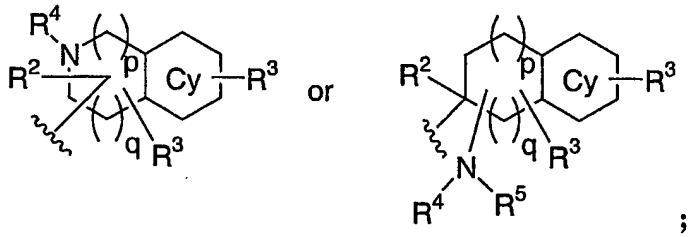
(I)

or a pharmaceutically acceptable salt thereof;

wherein Z is selected from the group consisting of



Q is



Cy is selected from the group consisting of benzene, pyridine, pyrimidine, pyrazine, piperidine, piperazine, and cyclohexane, wherein Cy is substituted with one to three groups independently selected from R^3;

m is 0 or 1;
n is 0, 1, or 2;
p is 0, 1, or 2;
q is 0, 1, or 2;

X is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_nC_{3-8}$ cycloalkyl,
$(CH_2)_n$aryl,
$(CH_2)_n$heteroaryl,
$(CH_2)_n$heterocyclyl,
$(CH_2)_nC{\equiv}N$,
$(CH_2)_nCON(R^8R^8)$,
$(CH_2)_nCO_2R^8$,
$(CH_2)_nCOR^8$
$(CH_2)_nNR^8C(O)R^8$,
$(CH_2)_nNR^8CO_2R^8$,
$(CH_2)_nNR^8C(O)N(R^8)_2$,
$(CH_2)_nNR^8SO_2R^8$,
$(CH_2)_nS(O)_mR^8$,
$(CH_2)_nSO_2N(R^8)(R^8)$,
$(CH_2)_nOR^8$,
$(CH_2)_nOC(O)R^8$,
$(CH_2)_nOC(O)OR^8$,
$(CH_2)_nOC(O)N(R^8)_2$,
$(CH_2)_nN(R^8)(R^8)$, and
$(CH_2)_nNR^8SO_2N(R^8)(R^8)$;
wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R^6; and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

Y is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,

$(CH_2)_nC_{3-8}$ cycloalkyl,
$(CH_2)_n$aryl,
$(CH_2)_n$heterocyclyl, and
$(CH_2)_n$heteroaryl;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R^6; and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are optionally substituted with one to three groups selected from R^6 and oxo;

R^1 is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CHR^7)_n$-C_{3-6} cycloalkyl,
$(CHR^7)_n$-$O(CHR^7)$aryl,
$(CHR^7)_n$aryl, and
$(CHR^7)_n$heteroaryl;
in which aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^6; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^2 is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_nC_{3-6}$ cycloalkyl, and
$(CH_2)_n$-aryl;

each R^3 is independently selected from
hydrogen,
C_{1-8} alkyl,
$(CH_2)_n$-aryl,
$(CH_2)_nC_{3-7}$ cycloalkyl,
$(CH_2)_n$-heteroaryl,
halo,
OR^7,
$NHSO_2R^7$,

$N(R^7)_2$,
$C{\equiv}N$,
CO_2R^7,
$C(R^7)(R^7)N(R^7)_2$,
NO_2,
$SO_2N(R^7)_2$,
$S(O)_mR^7$,
CF_3, and
OCF_3;

R^4 and R^5 are each independently selected from the group consisting of
hydrogen,
$C_{1\text{-}10}$ alkyl, and
$C_{3\text{-}8}$ cycloalkyl;

or R^4 and R^5 together with the nitrogen to which they are attached form a 5- to 8-membered ring optionally containing an additional heteroatom selected from O, S, and NR^7;

wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^6 is selected from the group consisting of
$C_{1\text{-}8}$ alkyl,
$(CH_2)_n$-aryl,
$(CH_2)_nC_{3\text{-}7}$ cycloalkyl,
$(CH_2)_n$-heteroaryl,
halo,
OR^7,
$NHSO_2R^7$,
$N(R^7)_2$,
$C{\equiv}N$,
CO_2R^7,
$C(R^7)(R^7)N(R^7)_2$,
NO_2,
$SO_2N(R^7)_2$,

$S(O)_mR^7$,
CF_3, and
OCF_3;

each R^7 is independently selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_n$-aryl, and
$(CH_2)_nC_{3-7}$ cycloalkyl;

each R^8 is independently selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_n$-aryl,
$(CH_2)_n$-heteroaryl, and
$(CH_2)_nC_{3-7}$ cycloalkyl;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^6; and alkyl, cycloalkyl, and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo; or two R^8 groups together with the atoms to which they are attached form a 5- to 8-membered mono- or bi-cyclic ring system optionally containing an additional heteroatom selected from O, S, and NR^7;

R^9 is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_n$-C_{3-6} cycloalkyl,
$(CH_2)_n$heterocyclyl,
$(CH_2)_n$aryl, and
$(CH_2)_n$heteroaryl;

in which aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^6; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^{10} is C_{1-6} alkyl unsubstituted or substituted with one to three fluoro groups; and

each R^{11} is independently hydrogen or C_{1-4} alkyl.

These compounds are effective as melanocortin receptor agonists and are particularly effective as selective melanocortin-4 receptor (MC-4R) agonists. They are therefore useful for the treatment and/or prevention of disorders responsive to the activation of MC-4R, such as obesity, diabetes as well as male and/or female sexual dysfunction, in particular, male erectile dysfunction.

The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention and a pharmaceutically acceptable carrier.

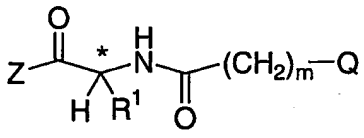
The present invention also relates to methods for the treatment or prevention of disorders, diseases, or conditions responsive to the activation of the melanocortin receptor in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

The present invention also relates to methods for the treatment or prevention of obesity, diabetes mellitus, and male and/or female sexual dysfunction by administering the compounds and pharmaceutical compositions of the present invention.

The present invention also relates to methods for treating erectile dysfunction by administering the compounds and pharmaceutical compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

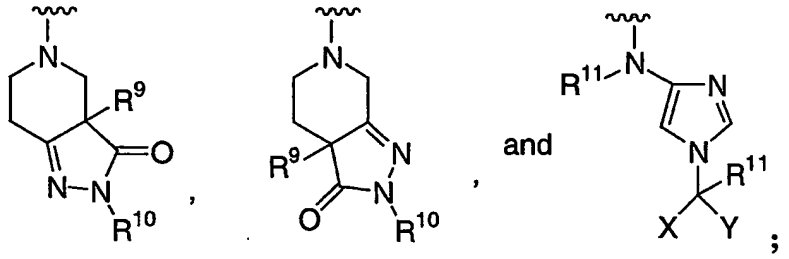
The present invention relates to compounds useful as melanocortin receptor agonists. Representative compounds of the present invention are described by structural formula (I):



(I)

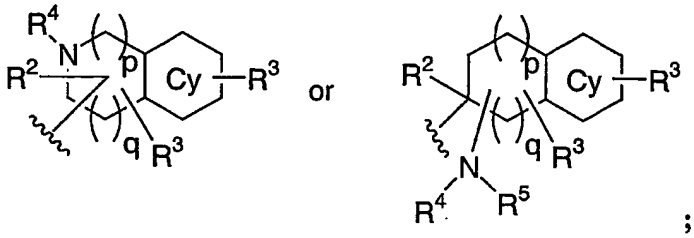
or a pharmaceutically acceptable salt thereof;

wherein Z is selected from the group consisting of



;

Q is



;

Cy is selected from the group consisting of benzene, pyridine, pyrimidine, pyrazine, piperidine, piperazine, and cyclohexane, wherein Cy is substituted with one to three groups independently selected from R^3;

m is 0 or 1;
n is 0, 1, or 2;
p is 0, 1, or 2;
q is 0, 1, or 2;

X is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_nC_{3-8}$ cycloalkyl,
$(CH_2)_n$aryl,
$(CH_2)_n$heteroaryl,
$(CH_2)_n$heterocyclyl,
$(CH_2)_nC{\equiv}N$,

$(CH_2)_nCON(R^8R^8)$,
$(CH_2)_nCO_2R^8$,
$(CH_2)_nCOR^8$
$(CH_2)_nNR^8C(O)R^8$,
$(CH_2)_nNR^8CO_2R^8$,
$(CH_2)_nNR^8C(O)N(R^8)_2$,
$(CH_2)_nNR^8SO_2R^8$,
$(CH_2)_nS(O)_mR^8$,
$(CH_2)_nSO_2N(R^8)(R^8)$,
$(CH_2)_nOR^8$,
$(CH_2)_nOC(O)R^8$,
$(CH_2)_nOC(O)OR^8$,
$(CH_2)_nOC(O)N(R^8)_2$,
$(CH_2)_nN(R^8)(R^8)$, and
$(CH_2)_nNR^8SO_2N(R^8)(R^8)$;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R^6; and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

Y is selected from the group consisting of
hydrogen,
$C_{1\text{-}8}$ alkyl,
$(CH_2)_nC_{3\text{-}8}$ cycloalkyl,
$(CH_2)_n$aryl,
$(CH_2)_n$heterocyclyl, and
$(CH_2)_n$heteroaryl;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R^6; and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are optionally substituted with one to three groups selected from R^6 and oxo;

R^1 is selected from the group consisting of
hydrogen,
$C_{1\text{-}8}$ alkyl,
$(CHR^7)_n$-$C_{3\text{-}6}$ cycloalkyl,

$(CHR^7)_n$-O(CHR^7)aryl,
$(CHR^7)_n$aryl, and
$(CHR^7)_n$heteroaryl;

in which aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^6; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^2 is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_nC_{3-6}$ cycloalkyl, and
$(CH_2)_n$-aryl;

each R^3 is independently selected from
hydrogen,
C_{1-8} alkyl,
$(CH_2)_n$-aryl,
$(CH_2)_nC_{3-7}$ cycloalkyl,
$(CH_2)_n$-heteroaryl,
halo,
OR^7,
$NHSO_2R^7$,
$N(R^7)_2$,
C≡N,
CO_2R^7,
$C(R^7)(R^7)N(R^7)_2$,
NO_2,
$SO_2N(R^7)_2$,
$S(O)_mR^7$,
CF_3, and
OCF_3;

R^4 and R^5 are each independently selected from the group consisting of
hydrogen,

C_{1-10} alkyl, and
C_{3-8} cycloalkyl;

or R^4 and R^5 together with the nitrogen to which they are attached form a 5- to 8-membered ring optionally containing an additional heteroatom selected from O, S, and NR^7;

wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^6 is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_n$-aryl,
$(CH_2)_nC_{3-7}$ cycloalkyl,
$(CH_2)_n$-heteroaryl,
halo,
OR^7,
$NHSO_2R^7$,
$N(R^7)_2$,
$C\equiv N$,
CO_2R^7,
$C(R^7)(R^7)N(R^7)_2$,
NO_2,
$SO_2N(R^7)_2$,
$S(O)_mR^7$,
CF_3, and
OCF_3;

each R^7 is independently selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_n$-aryl, and
$(CH_2)_nC_{3-7}$ cycloalkyl;

each R^8 is independently selected from the group consisting of
hydrogen,

C_{1-8} alkyl,
$(CH_2)_n$-aryl,
$(CH_2)_n$-heteroaryl, and
$(CH_2)_nC_{3-7}$ cycloalkyl;

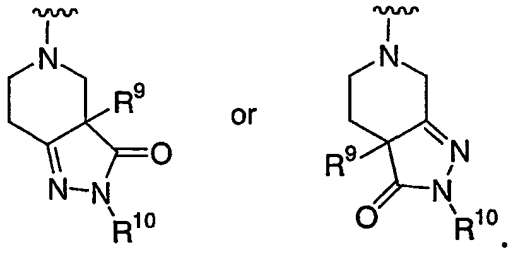
wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^6; and alkyl, cycloalkyl, and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo; or two R^8 groups together with the atoms to which they are attached form a 5- to 8-membered mono- or bi-cyclic ring system optionally containing an additional heteroatom selected from O, S, and NR^7;

R^9 is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_n$-C_{3-6} cycloalkyl,
$(CH_2)_n$heterocyclyl,
$(CH_2)_n$aryl, and
$(CH_2)_n$heteroaryl;

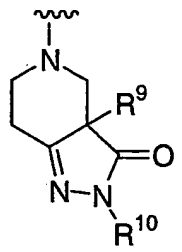
in which aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^6; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^{10} is C_{1-6} alkyl unsubstituted or substituted with one to three fluoro groups; and each R^{11} is independently hydrogen or C_{1-4} alkyl.

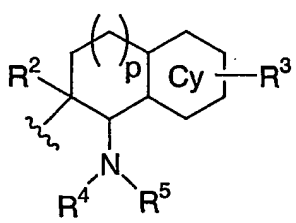
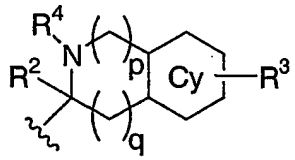
In one embodiment of the compounds of the present invention, Z is



In a class of this embodiment, Z is



In a second embodiment of the compounds of the present invention, Q is


or


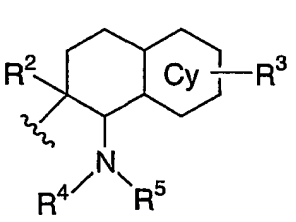
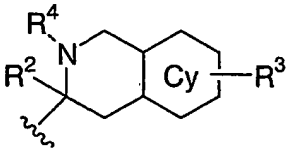
wherein

p is 1 or 2;

q is 0 or 1; and

R^2, R^3, R^4, and R^5 are as defined above.

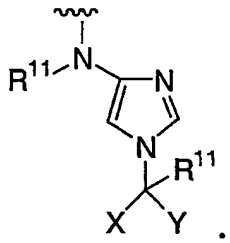
In a class of this second embodiment of the present invention, Q is


or

;

wherein m = 0 and

R^2, R^3, R^4, and R^5 are as defined above.

In a third embodiment of the compounds of the present invention, Z is



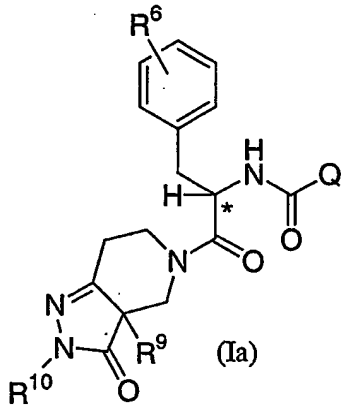
In a class of this embodiment, X is $(CH_2)_n$-aryl, $(CH_2)_n$-heteroaryl, $(CH_2)_n$-heterocyclyl, $(CH_2)_nC(O)N(R^8)(R^8)$, $(CH_2)_nCO_2R^8$, $(CH_2)_nOR^8$, $(CH_2)_nNHC(O)R^8$, or $(CH2)nNR^8SO_2R^8$, wherein aryl and heteroaryl are optionally substituted with one to three groups selected from R^6; heterocyclyl is optionally substituted with one to three groups selected from R^6 and oxo; and the $(CH_2)_n$ group is optionally substituted with one to three groups selected from R^7, halo, $S(O)_mR^7$, $N(R^7)_2$, and OR^7; and Y is C_{1-8} alkyl, $(CH_2)_nC_{5-7}$ cycloalkyl, $(CH_2)_n$-aryl, $(CH_2)_n$-heterocyclyl, or $(CH_2)_n$-heteroaryl, wherein aryl and heteroaryl are optionally substituted with one to three groups selected from R^6; and $(CH_2)_n$, alkyl, cycloalkyl, and heterocyclyl are optionally substituted with one to three groups selected from R^6 and oxo. In a subclass of this class, Y is cyclohexyl, cycloheptyl, cyclopentyl, or C_{1-6} alkyl, each of which is unsubstituted or substituted with one to three groups selected from R^6 and oxo. In a further subclass of this class, each R^{11} is independently hydrogen or methyl and Y is cyclohexyl or C_{1-6} alkyl, wherein the cyclohexyl and alkyl groups are unsubstituted or substituted with one to three groups selected from R^6 and oxo.

In a fourth embodiment of the compounds of the present invention, R^1 is $CH(R^7)$-aryl, $CH(R^7)$-heteroaryl, or $CH(R^7)OCH(R^7)$-aryl, wherein aryl and heteroaryl are unsubstituted or substituted with one or two R^6 groups. In a class of this embodiment, R^1 is benzyl or benzyloxymethyl unsubstituted or substituted with one or two groups selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, and OCF_3. In a subclass of this class, R^1 is 4-chlorobenzyl, 4-fluorobenzyl, or 4-methoxybenzyl.

In a fifth embodiment of the compounds of the present invention, R^2 is hydrogen or methyl.

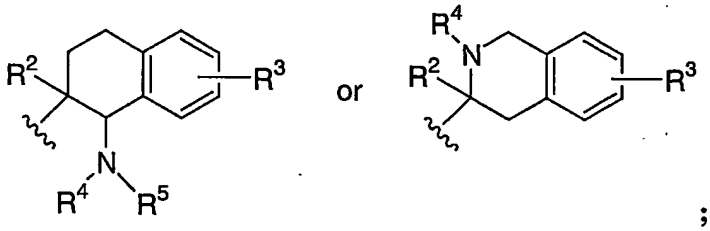
In a sixth embodiment of the compounds of the present invention, the carbon atom marked with * has the *R* configuration.

In yet a further embodiment of the compounds of the present invention, there are provided compounds of formula Ia:



(Ia)

wherein Q is



;

R^2 is hydrogen or methyl;

R^3 is as defined above;

R^4 and R^5 are each independently selected from the group consisting of

hydrogen,

C_{1-6} alkyl, and

C_{5-6} cycloalkyl;

or R^4 and R^5 together with the nitrogen to which they are attached form a 5- to 7-membered ring optionally containing an additional heteroatom selected from O, S, and NR^7;

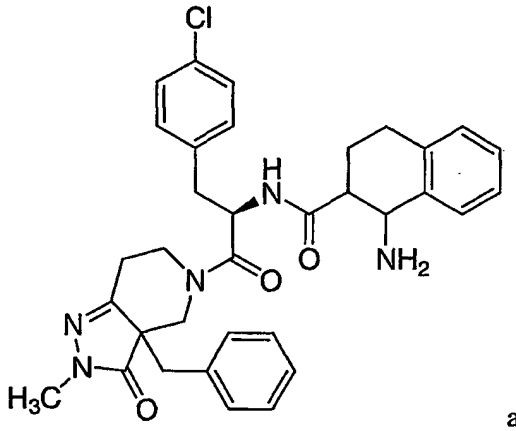
wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^6 is chloro, fluoro, CF_3, methoxy, or C_{1-4} alkyl;
R^7 is hydrogen, C_{1-8} alkyl, or C_{3-6} cycloalkyl;

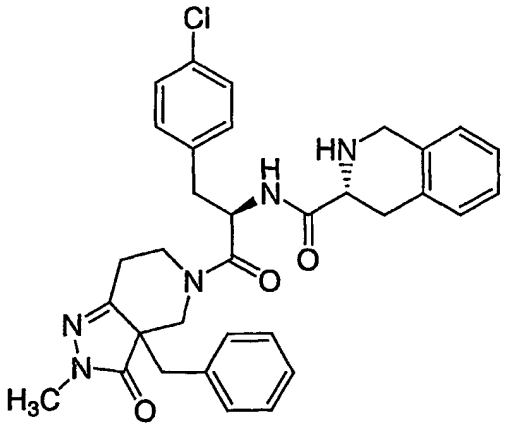
R^9 is phenyl, benzyl, pyridyl, or pyridylmethyl, each of which is unsubstituted or substituted with one or two R^6 groups; and
R^{10} is methyl or CH_2CF_3.

In yet a further embodiment of compounds of formula Ia, the carbon atom marked with * has the *R* configuration.

Representative compounds of formula I are as follows:



and



;

or a pharmaceutically acceptable salt thereof.

The compounds of structural Formula I are effective as melanocortin receptor agonists and are particularly effective as selective agonists of the MC-4R. They are therefore useful for the treatment and/or prevention of disorders responsive to the activation of MC-4R, such as obesity, diabetes as well as male and/or female sexual dysfunction, in particular, erectile dysfunction, and further in particular, male erectile dysfunction.

Another aspect of the present invention provides a method for the treatment or prevention of obesity or diabetes in a mammal which comprises administering to said mammal an effective amount of a compound of formula I.

Another aspect of the present invention provides a method for the treatment or prevention of male or female sexual dysfunction including erectile dysfunction which comprises administering to a patient in need of such treatment or prevention an effective amount of a compound of formula I.

Yet another aspect of the present invention provides a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier.

Throughout the instant application, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term "aryl" includes phenyl and naphthyl.

The term "heteroaryl" includes mono- and bicyclic aromatic rings containing from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. "5- or 6-membered heteroaryl" are monocyclic heteroaromatic rings, examples thereof include thiazole, oxazole, thiophene, furan, pyrrole, imidazole, isoxazole, pyrazole, triazole, thiadiazole, tetrazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, and the like. Bicyclic heteroaromatic rings include, but are not limited to, benzothiadiazole, indole, benzothiophene, benzofuran, benzimidazole, benzisoxazole,

benzothiazole, quinoline, benzotriazole, benzoxazole, isoquinoline, purine, furopyridine and thienopyridine.

The term "5- or 6-membered carbocyclyl" is intended to include non-aromatic rings containing only carbon atoms such as cyclopentyl and cyclohexyl.

The term "5 and 6-membered heterocyclyl" is intended to include non-aromatic heterocycles containing one to four heteroatoms selected from nitrogen, oxygen and sulfur. Examples of a 5 or 6-membered heterocyclyl include piperidine, morpholine, thiamorpholine, pyrrolidine, imidazolidine, tetrahydrofuran, piperazine, and the like.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus for example, NR^7R^7 may represent NH_2, $NHCH_3$, $N(CH_3)CH_2CH_3$, and the like.

The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

"Erectile dysfunction" is a disorder involving the failure of a male mammal to achieve erection, ejaculation, or both. Symptoms of erectile dysfunction include an inability to achieve or maintain an erection, ejaculatory failure, premature ejaculation, or inability to achieve an orgasm. An increase in erectile dysfunction is often associated with age and is generally caused by a physical disease or as a side-effect of drug treatment.

By a melanocortin receptor "agonist" is meant an endogenous or drug substance or compound that can interact with a melanocortin receptor and initiate a pharmacological response characteristic of the melanocortin receptor. By a melanocortin receptor "antagonist" is meant a drug or a compound that opposes the melanocortin receptor-associated responses normally induced by another bioactive agent. The "agonistic" properties of the compounds of the present invention were

measured in the functional assay described below. The functional assay discriminates a melanocortin receptor agonist from a melanocortin receptor antagonist.

By "binding affinity" is meant the ability of a compound/drug to bind to its biological target, in the the present instance, the ability of a compound of formula I to bind to a melanocortin receptor. Binding affinities for the compounds of the present invention were measured in the binding assay described below and are expressed as IC50's.

"Efficacy" describes the relative intensity with which agonists vary in the response they produce even when they occupy the same number of receptors and with the same affinity. Efficacy is the property that enables drugs to produce responses. Properties of compounds/drugs can be categorized into two groups, those which cause them to associate with the receptors (binding affinity) and those that produce a stimulus (efficacy). The term "efficacy" is used to characterize the level of maximal responses induced by agonists. Not all agonists of a receptor are capable of inducing identical levels of maximal responses. Maximal response depends on the efficiency of receptor coupling, that is, from the cascade of events, which, from the binding of the drug to the receptor, leads to the desired biological effect.

The functional activities expressed as EC50's and the "agonist efficacy" for the compounds of the present invention at a particular concentration were measured in the functional assay described below.

Optical Isomers - Diastereoisomers - Geometric Isomers - Tautomers

Compounds of Formula I contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist as tautomers such as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into their individual diastereoisomers by, for example, fractional crystallization from a suitable solvent, for

example methanol or ethyl acetate or a mixture thereof, or via chiral chromatography using an optically active stationary phase.

Alternatively, any diastereoisomer of a compound of the general Formula I or Ia may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Particularly preferred are citric, fumaric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utility

Compounds of formula I are melanocortin receptor agonists and as such are useful in the treatment, control or prevention of diseases, disorders or conditions responsive to the activation of one or more of the melanocortin receptors including, but are not limited to, MC-1, MC-2, MC-3, MC-4, or MC-5. Such diseases, disorders or conditions include, but are not limited to, obesity (by reducing appetite, increasing metabolic rate, reducing fat intake or reducing carbohydrate craving), diabetes mellitus (by enhancing glucose tolerance, decreasing insulin resistance), hypertension, hyperlipidemia, osteoarthritis, cancer, gall bladder disease, sleep apnea, depression, anxiety, compulsion, neuroses, insomnia/sleep disorder, substance abuse, pain, male and female sexual dysfunction (including impotence, loss of libido and erectile dysfunction), fever, inflammation, immunemodulation, rheumatoid arthritis, skin tanning, acne and other skin disorders, neuroprotective and cognitive and memory enhancement including the treatment of Alzheimer's disease. Some compounds encompassed by formula I show highly selective affinity for the melanocortin-4 receptor relative to MC-1R, MC-2R, MC-3R, and MC-5R, which makes them especially useful in the prevention and treatment of obesity, as well as male and/or female sexual dysfunction, including erectile dysfunction.

Administration and Dose Ranges

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of Formula I are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from 0.01 milligram to about 100 milligrams per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained

release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.7 milligrams to about 3500 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

When treating diabetes mellitus and/or hyperglycemia, as well as other diseases or disorders for which compounds of formula I are useful, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.001 milligram to about 100 milligram per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.07 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

For the treatment of sexual dysfunction compounds of the present invention are given in a dose range of 0.001 milligram to about 100 milligram per kilogram of body weight, preferably as a single dose orally or as a nasal spray.

Combination Therapy

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

(a) insulin sensitizers including (i) PPARγ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, BRL49653 and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin;

(b) insulin or insulin mimetics;

(c) sulfonylureas, such as tolbutamide and glipizide;

(d) α-glucosidase inhibitors (such as acarbose),

(e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and other statins), (ii) sequestrants (cholestyramine, colestipol and a dialkylaminoalkyl derivatives of a cross-linked dextran), (ii) nicotinyl alcohol nicotinic acid or a salt thereof, (iii) proliferator-activater receptor α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), (iv) inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide, (v) probucol, (vi) vitamin E, and (vii) thyromimetics;

(f) PPARδ agonists, such as those disclosed in WO97/28149;

(g) antiobesity compounds, such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, or β3 adrenergic receptor agonists;

(h) feeding behavior modifying agents, such as neuropeptide Y antagonists (e.g. neuropeptide Y5) such as those disclosed in WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822 and WO 97/20823;

(i) PPARα agonists such as described in WO 97/36579 by Glaxo;

(j) PPARγ antagonists as described in WO97/10813;

(k) serotonin reuptake inhibitors such as fluoxetine and sertraline;

(l) growth hormone secretagogues such as MK-0677; and

(m) agents useful in the treatment of male and/or female sexual dysfunction, such as type V cyclic-GMP-specific phosphodiesterase (PDE-V) inhibitors, such as sildenafil and IC-351; α_2-adrenergic receptor antagonists, such as phentolamine mesylate; and dopamine receptor agonists, such as apomorphine.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose

or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

In the Schemes and Examples below, various reagent symbols and abbreviations have the following meanings:

BOC (boc)	t-butyloxycarbonyl
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Bu	butyl
calc.	calculated
CBZ (Cbz)	benzyloxycarbonyl
DEAD	diethyl azodicarboxylate
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide

EDC	1-(3-dimethylaminopropyl)3-ethylcarbodiimide HCl
eq.	equivalent(s)
ESI-MS	electron spray ion-mass spectroscopy
Et	ethyl
EtOAc	ethyl acetate
HATU	*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-b] pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate N-oxide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
LDA	lithium diisopropylamide
MC-*x*R	melanocortin receptor (*x* being a number)
Me	methyl
MF	molecular formula
Ms	methanesulfonyl
NMM	N-methylmorpholine
OIC	octahydroindole-2-carboxylic acid
Ph	phenyl
Phe	phenylalanine
Pr	propyl
PyBrop	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
Tic(OH)	7-hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
TLC	thin-layer chromatography

Preparation of Compounds of the Invention

The novel compounds of the present invention can be prepared according to the procedure of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming

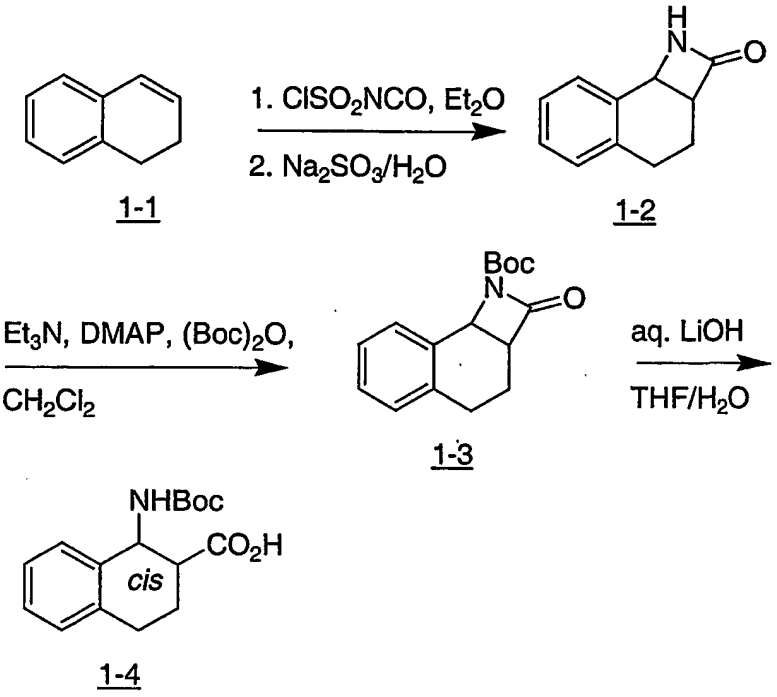
the only genus that is considered as the invention. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

The following Schemes and Examples describe procedures for making representative compounds of the present invention. Moreover, by utilizing the procedures and intermediates described in detail in PCT International Application Publication Nos. WO 99/64002 (16 December 1999), WO 97/24369 (10 July 1997), WO 98/58949 (30 December 1998), and WO 99/08699 (25 February 1999), each of which is incorporated by reference herein in its entirety, in conjunction with the disclosure contained herein, one of ordinary skill in the art can readily prepare additional compounds of the present invention claimed herein.

The phrase "standard peptide coupling reaction conditions" means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in a inert solvent such as dichloromethane in the presence of a catalyst such as HOBT. The use of protecting groups for amine and carboxylic acid to facilitate the desired reaction and minimize undesired reactions is well documented. Conditions required to remove protecting groups are found in standard textbooks such as Greene, T, and Wuts, P. G. M., *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, NY, 1991. CBZ and BOC are commonly used protecting groups in organic synthesis, and their removal conditions are known to those skilled in the art. For example, CBZ may be removed by catalytic hydrogenation with hydrogen in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as ethanol. In cases where catalytic hydrogenation is contraindicated due to the presence of other potentially reactive functionalities, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid, or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out in a solvent such as methylene chloride, methanol, or ethyl acetate, with a strong acid, such as trifluoroacetic acid, hydrochloric acid, or hydrogen chloride gas.

It is understood that in some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products.

SCHEME 1



Step A:

To a solution of 1,2-dihydronaphthalene (1-1) (4.0 g, 30.7 mmole) in ether (40 ml) was added a solution of chlorosulfonyl isocyanate (2.7 ml, 31.0 mmole) in ether (40 ml). After stirring at 0°C for 0.5 hour, the reaction mixture was allowed to warm up to room temperature and continued to stir for another 4 hours. The reaction mixture was poured into 20% of sodium sulfite (80 ml) and stirred vigorously for one hour. After addition of ethyl acetate, the organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated to give a colorless oil (4.3 g) which was crystallized from a small amount of hexane (3 ml) to give 1-2 as a white solid (3.0 g). ESI-MS calc. for $C_{11}H_{11}NO$: 173.1; Found: 174 (M+H), 196 (M+Na), 347 (2M+1), 369 (2M+Na).

Step B:

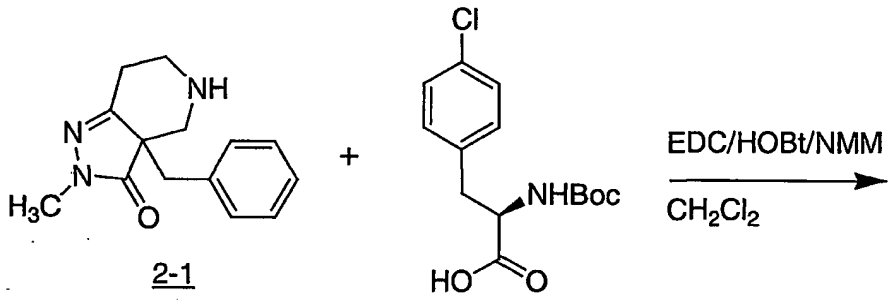
To a solution of lactam 1-2 (2.0 g, 11.56 mmol) in methylene chloride (100ml) containing triethylamine (3.51 g, 34.7 mmol) and DMAP (141 mg, 1.156

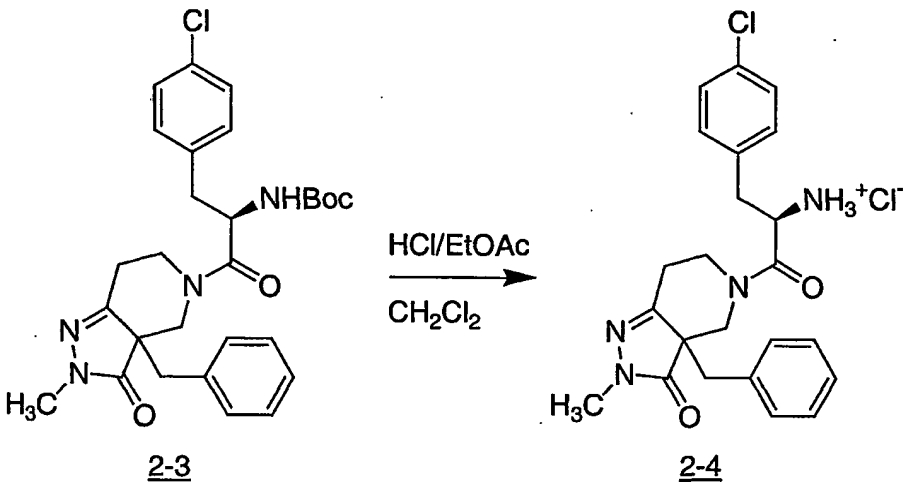
mmol) was added $(Boc)_2O$ (2.78 g, 12.72 mmol). After stirring the reaction mixture overnight, solvent was removed, the residue diluted with methylene chloride, washed with brine, dried and concentrated to give 3.4 g of the product 1-3: ESI-MS calc. for $C_{16}H_{19}NO_3$: 273.1; Found: 296 (M+Na).

Step C:

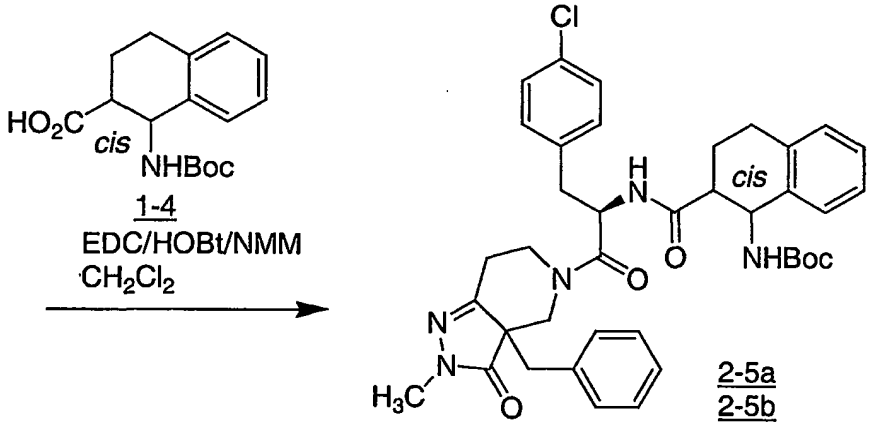
To a solution of Boc-lactam 1-3 (1.76 g, 6.4 mmol) in THF (20 ml) and water (15 ml) was added aqueous LiOH (1.35g, 32.2 mmol). After stirring the reaction mixture overnight at 23°C, THF was removed, the aqueous layer washed with ether, acidified with aqueous $NaHSO_4$ and extracted with methylene chloride. The organic layer was dried and concentrated to furnish *cis* Boc-acid 1-4 (1.76 g): ESI-MS calc. for $C_{16}H_{21}NO_4$: 291.2; Found: 314 (M+Na).

SCHEME 2

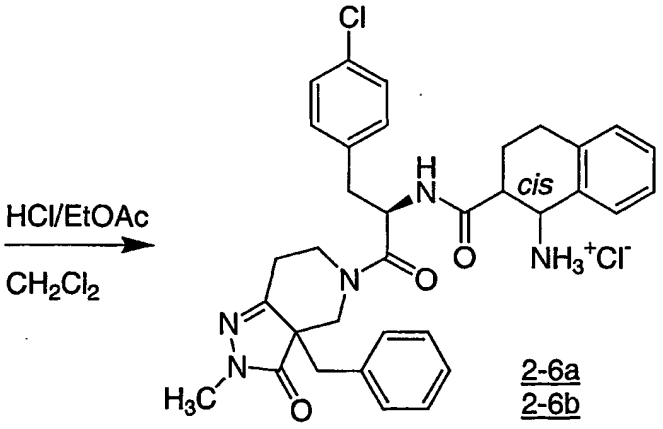




2-3 2-4



2-5a
2-5b



2-6a
2-6b

EXAMPLES 1 and 2

(Compounds 2-6a and 2-6b)

Step A:

To a solution of Boc-4-Cl-D-Phe (2-2) (897 mg, 0.3 mmol) in methylene chloride (15 ml) were added EDC (958 mg, 5 mmol), HOBT (675 mg, 5 mmol) and NMM (1.21 g, 12 mmol). After stirring the reaction mixture for 5 minutes, amine 2-1 (for the preparation of 2-1, see WO 98/58949, published 30 December 1998) (1.07 g, 3 mmol) was added. The reaction mixture was allowed to stir overnight, diluted with methylene chloride (50 ml), washed with water, dilute aq. HCl, aq. $NaHCO_3$ and brine. The organic layer was dried, concentrated, and the residue purified by preparative thin-layer chromatography using CH_2Cl_2/acetone (9/1) as eluant to give pure 2-3 (1.28 g. 2.42 mmol): ESI-MS calc. for $C_{28}H_{33}N_4O_4Cl$: 524; Found 525 (M+1).

Step B:

To a solution of 2-3 (1.28 g, 2.42 mmol) in methylene chloride (5 ml) was added saturated HCl/EtOAc (5 ml) solution. After stirring the reaction mixture for 0.5 hr at 23°C, the mixture was concentrated and lyophilized from benzene and methanol to give pure 2-4 (1.017 g. 2.4 mmol): ESI-MS calc. for $C_{23}H_{25}N_2O_2Cl$: 424; Found 425 (M+1).

Step C:

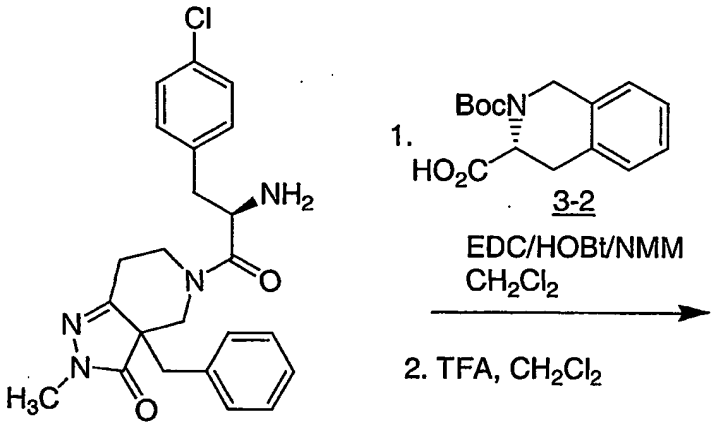
To a solution of 2-4 (212 mg, 0.5 mmol) in methylene chloride were added EDC (191 mg, 1 mmol), HOBT (135 mg, 1 mmol) and NMM (406 mg, 4 mmol). After stirring the reaction mixture for 5 minutes, Boc-amino acid 1-4 (145.5 mg, 0.5 mmol) was added. The reaction was stirred overnight at room temperature, diluted with methylene chloride (50 ml), washed with water, diluted aq. HCl, aq. $NaHCO_3$ and brine. The organic layer was dried, concentrated and purified by column chromatography (silica-gel, 10% acetone in CH_2Cl_2) to give 2-5a [higher R_f product, 100 mg, ESI-MS calc. for $C_{39}H_{44}N_5O_5Cl$: 697; Found 698 (M+1)] and 2-5b (lower R_f product, 130 mg, ESI-MS calc. for $C_{39}H_{44}N_5O_5Cl$: 697; Found 698 (M+1)].

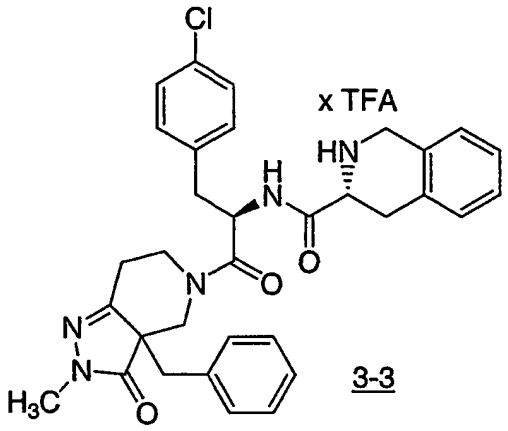
Step D:

To a solution of 2-5a (100mg) in methylene chloride (2 ml) was added a solution of saturated HCl/EtOAc (3 ml). After stirring the solution for 0.5 hr at room temperature, the mixture was concentrated and lyophilized from benzene/methanol to give 2-6a (80 mg): ESI-MS calc. for $C_{34}H_{36}N_5O_5Cl$: 597; Found 598 (M+1).

To a solution of 2-5b (130 mg) in methylene chloride (2 ml) was added a solution of saturated HCl/EtOAc (3 ml). After stirring the solution for 0.5 hr at room temperature, the mixture was concentrated and lyophilized from benzene/methanol to give 2-6b (100 mg): ESI-MS calc. for $C_{34}H_{36}N_5O_5Cl$: 597; Found 598 (M+1).

SCHEME 3





3-3

EXAMPLE 3

(Compound 3-3)

To a solution of amine 3-1 (110.1 mg, 0.259 mmol) in methylene chloride (5.0 mL) were added Boc-amino acid 3-2 (86.2 mg, 0.311 mmol), HOBt (42.0 mg, 0.311 mmol), EDC (59.6 mg, 0.311 mmol), and NMM (0.10 mL, 0.909 mmol). The mixture was stirred at room temperature overnight and quenched with EtOAc (50 mL). The organic solution was washed with 5 % aq HCl solution (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), and dried over anhydrous Na_2SO_4, and concentrated. The Boc-protected product was dissolved in methylene chloride (4.0 mL) and TFA (1.0 mL) was added to the solution. The mixture was stirred at room temperature for 30 min, and solvents were then removed under vacuum. Ether was added and solid was filtered and washed with ether and dried to yield 3-3 as a white solid (87.5 mg).

Mass spectrum: 584 (M + 1).

BIOLOGICAL ASSAYS

A. Binding Assay. The membrane binding assay was used to identify competitive inhibitors of ^{125}I-NDP-alpha-MSH binding to cloned human MCRs expressed in L- or CHO- cells.

Cell lines expressing melanocortin receptors were grown in T-180 flasks containing selective medium of the composition: 1 L Dulbecco's modified Eagles Medium (DMEM) with 4.5 g L-glucose, 25 mM Hepes, without sodium pyruvate, (Gibco/BRl); 100 ml 10% heat-inactivated fetal bovine serum (Sigma); 10 ml 10,000 unit/ml penicillin & 10,000 ug/ml streptomycin (Gibco/BRl); 10 ml 200 mM L-glutamine (Gibco/BRl); 1 mg/ml Geneticin (G418) (Gibco/BRl). The cells were grown at 37°C with CO_2 and humidity control until the desired cell density and cell number was obtained.

The medium was poured off and 10 mls/monolayer of enzyme-free dissociation media (Specialty Media Inc.) was added. The cells were incubated at 37°C for 10 minutes or until cells sloughed off when flask was banged against hand.

The cells were harvested into 200 ml centrifuge tubes and spun at 1000 rpm, 4° C, for 10 min. The supernatant was discarded and the cells were resuspended in 5 mls/monolayer membrane preparation buffer having the composition: 10 mM Tris pH 7.2-7.4; 4 ug/ml Leupeptin (Sigma); 10 uM Phosphoramidon (Boehringer Mannheim); 40 ug/ml Bacitracin (Sigma); 5 ug/ml Aprotinin (Sigma); 10 mM Pefabloc (Boehringer Mannheim). The cells were homogenized with motor-driven dounce (Talboy setting 40), using 10 strokes and the homogenate centrifuged at 6,000 rpm, 4°C, for 15 minutes.

The pellets were resuspended in 0.2 mls/monolayer membrane prep buffer and aliquots were placed in tubes (500-1000 ul/tube) and quick frozen in liquid nitrogen and then stored at -80°C.

Test compounds or unlabelled NDP-α-MSH was added to 100 µL of membrane binding buffer to a final concentration of 1 µM. The membrane binding buffer had the composition: 50 mM Tris pH 7.2; 2 mM $CaCl_2$; 1 mM $MgCl_2$; 5 mM KCl; 0.2% BSA; 4 ug/ml Leupeptin (SIGMA); 10 uM Phosphoramidon (Boehringer Mannheim); 40 ug/ml Bacitracin (SIGMA); 5 ug/ml Aprotinin (SIGMA); and 10 mM Pefabloc (Boehringer Mannheim). One hundred µl of membrane binding buffer containing 10-40 ug membrane protein was added, followed by 100 µM 125I-NDP-α-

MSH to final concentration of 100 pM. The resulting mixture was vortexed briefly and incubated for 90-120 min at room temp while shaking.

The mixture was filtered with Packard Microplate 196 filter apparatus using Packard Unifilter 96-well GF/C filter with 0.1% polyethyleneimine (Sigma). The filter was washed (5 times with a total of 10 ml per well) at room temperature with filter wash having the composition: 50mM Tris-HCl pH 7.2 and 20 mM NaCl. The filter was dried, and the bottom sealed and 50 ul of Packard Microscint-20 was added to each well. The top was sealed and the radioactivity quantitated in a Packard Topcount Microplate Scintillation counter.

B. Functional assay. Functional cell based assays were developed to discriminate melanocortin receptor agonists from antagonists.

Cells (for example, CHO- or L-cells or other eukaryotic cells) expressing a human melanocortin receptor (see e.g. Yang-YK; Ollmann-MM; Wilson-BD; Dickinson-C; Yamada-T; Barsh-GS; Gantz-I; Mol. Endocrinol. 1997, 11(3): 274-80) were dissociated from tissue culture flasks by rinsing with Ca and Mg free phosphate buffered saline (14190-136, Life Technologies, Gaithersburg, MD) and detached following 5 minutes incubation at 37°C with enzyme free dissociation buffer (S-014-B, Specialty Media, Lavellette, NJ). Cells were collected by centrifugation and resuspended in Earle's Balanced Salt Solution (14015-069, Life Technologies, Gaithersburg, MD) with additions of 10 mM HEPES pH 7.5, 5 mM $MgCl_2$, 1 mM glutamine and 1 mg/ml bovine serum albumin. Cells were counted and diluted to 1 to 5 x 10^6/ml. The phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine was added to cells to 0.6 mM.

Test compounds were diluted in dimethylsulfoxide (DMSO) (10^{-5} to 10^{-10} M) and 0.1 volume of compound solution was added to 0.9 volumes of cell suspension; the final DMSO concentration was 1%. After room temperature incubation for 45 min., cells were lysed by incubation at 100°C for 5 min. to release accumulated cAMP.

cAMP was measured in an aliquot of the cell lysate with the Amersham (Arlington Heights, IL) cAMP detection assay (RPA556). The amount of cAMP production which resulted from an unknown compound was compared to that amount of cAMP produced in response to alpha-MSH which was defined as a 100 % agonist. The EC_{50} is defined as the compound concentration which results in half maximal stimulation, when compared to its own maximal level of stimulation.

Antagonist assay: Antagonist activity was defined as the ability of a compound to block cAMP production in response to alpha-MSH. Solution of test compounds and suspension of receptor containing cells were prepared and mixed as described above; the mixture was incubated for 15 min., and an EC50 dose (approximately 10 nM alpha-MSH) was added to the cells. The assay was terminated at 45 min. and cAMP quantitated as above. Percent inhibition was determined by comparing the amount of cAMP produced in the presence to that produced in the absence of test compound.

C. In vivo food intake models.

1) Overnight food intake. Sprague Dawley rats are injected intracerebroventricularly with a test compound in 400 nL of 50% propylene glycol/artificial cerebrospinal fluid one hour prior to onset of dark cycle (12 hours). Food intake is determined using a computerized system in which each rat's food is placed on a computer monitored balance. Cumulative food intake for 16 hours post compound administration is measured.

2) Food intake in diet induced obese mice. Male C57/B16J mice maintained on a high fat diet (60% fat calories) for 6.5 months from 4 weeks of age are are dosed intraperitoneally with test compound. Food intake and body weight are measured over an eight day period. Biochemical parameters relating to obesity, including leptin, insulin, triglyceride, free fatty acid, cholesterol and serum glucose levels are determined.

D. Rat Ex Copula Assay

Sexually mature male Caesarian Derived Sprague Dawley (CD) rats (over 60 days old) are used with the suspensory ligament surgically removed to prevent retraction of the penis back into the penile sheath during the ex copula evaluations. Animals receive food and water *ad lib* and are kept on a normal light/dark cycle. Studies are conducted during the light cycle.

1) Conditioning to Supine Restraint for Ex Copula Reflex Tests. This conditioning takes ~ 4 days. On Day 1, the animals are placed in a darkened restrainer and left for 15 - 30 minutes. On Day 2, the animals are restrained in a supine position in the restrainer for 15 - 30 minutes. On Day 3, the animals are restrained in the supine position with the penile sheath retracted for 15 - 30 minutes. On Day 4, the

animals are restrained in the supine position with the penile sheath retracted until penile responses are observed. Some animals require additional days of conditioning before they are completely acclimated to the procedures; non-responders are removed from further evaluation. After any handling or evaluation animals are given a treat to ensure positive reinforcement.

2) Ex Copula Reflex Tests. Rats are gently restrained in a supine position with their anterior torso placed inside a cylinder of adequate size to allow for normal head and paw grooming. For a 400-500 gram rat, the diameter of the cylinder is approximately 8 cm. The lower torso and hind limbs are restrained with a non-adhesive material (vetrap). An additional piece of vetrap with a hole in it, through which the glans penis will be passed, is fastened over the animal to maintain the preputial sheath in a retracted position. Penile responses will be observed, typically termed *ex copula* genital reflex tests. Typically, a series of penile erections will occur spontaneously within a few minutes after sheath retraction. The types of normal reflexogenic erectile responses include elongation, engorgement, cup and flip. An elongation is classified as an extension of the penile body. Engorgement is a dilation of the glans penis. A cup is defined as an intense erection where the distal margin of the glans penis momentarily flares open to form a cup. A flip is a dorsiflexion of the penile body.

Baseline and or vehicle evaluations are conducted to determine how and if an animal will respond. Some animals have a long duration until the first response while others are non-responders altogether. During this baseline evaluation latency to first response, number and type of responses are recorded. The testing time frame is 15 minutes after the first response.

After a minimum of 1 day between evaluations, these same animals are administered the test compound at 20 mg/kg and evaluated for penile reflexes. All evaluations are videotaped and scored later. Data are collected and analyzed using paired 2 tailed t-tests to compared baseline and/ or vehicle evaluations to drug treated evaluations for individual animals. Groups of a minimum of 4 animals are utilized to reduce variability.

Positive reference controls are included in each study to assure the validity of the study. Animals can be dosed by a number of routes of administration depending on the nature of the study to be performed. The routes of administration includes intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and intracerebral-ventricular (ICV).

E. Models of Female Sexual Dysfunction

Rodent assays relevant to female sexual receptivity include the behavioral model of lordosis and direct observations of copulatory activity. There is also a urethrogenital reflex model in anesthetized spinally transected rats for measuring orgasm in both male and female rats. These and other established animal models of female sexual dysfunction are described in McKenna KE et al., A Model For The Study of Sexual Function In Anesthetized Male And Female Rats, Am. J. Physiol. (Regulatory Integrative Comp. Physiol 30): R1276-R1285, 1991; McKenna KE et al., Modulation By Peripheral Serotonin of The Threshold For Sexual Reflexes In Female Rats, Pharm. Bioch. Behav., 40:151-156, 1991; and Takahashi LK et al., Dual Estradiol Action In The Diencephalon And The Regulation Of Sociosexual Behavior In Female Golden Hamsters, Brain Res., 359:194-207, 1985.

Representative compounds of the present invention were tested and found to bind to the melanocortin-4 receptor. These compounds were generally found to have IC_{50} values less than 2 μM. Representative compounds of the present invention were also tested in the functional assay and found generally to activate the melanocortin-4 receptor with EC_{50} values less than 1 μM.

EXAMPLES OF A PHARMACEUTICAL COMPOSITION

As a specific embodiment of an oral composition of a composition of the present invention, 5 mg of Example 1, 2, or 3 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

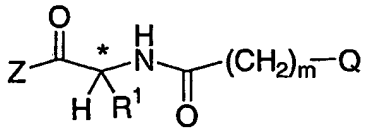
As another specific embodiment of an oral composition of a compound of the present invention, 2.5 mg of Example 1, 2, or 3 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove may be applicable as a

consequence of variations in the responsiveness of the mammal being treated for severity of bone disorders caused by resorption, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

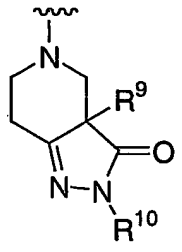
1. A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof;

wherein Z is selected from the group consisting of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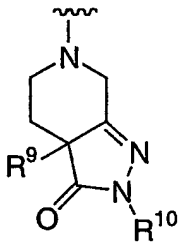
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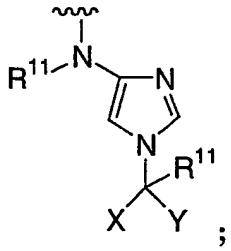
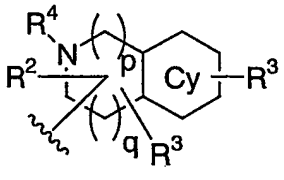
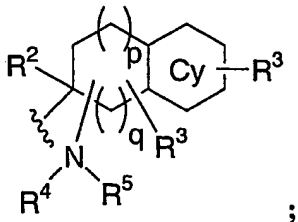

;

Q is


or

;

Cy is selected from the group consisting of benzene, pyridine, pyrimidine, pyrazine, piperidine, piperazine, and cyclohexane, wherein Cy is substituted with one to three groups independently selected from R^3;

m is 0 or 1;
n is 0, 1, or 2;
p is 0, 1, or 2;
q is 0, 1, or 2;

X is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_nC_{3-8}$ cycloalkyl,
$(CH_2)_n$aryl,
$(CH_2)_n$heteroaryl,
$(CH_2)_n$heterocyclyl,
$(CH_2)_nC{\equiv}N$,
$(CH_2)_nCON(R^8R^8)$,
$(CH_2)_nCO_2R^8$,
$(CH_2)_nCOR^8$
$(CH_2)_nNR^8C(O)R^8$,
$(CH_2)_nNR^8CO_2R^8$,
$(CH_2)_nNR^8C(O)N(R^8)_2$,
$(CH_2)_nNR^8SO_2R^8$,
$(CH_2)_nS(O)_mR^8$,
$(CH_2)_nSO_2N(R^8)(R^8)$,
$(CH_2)_nOR^8$,
$(CH_2)_nOC(O)R^8$,
$(CH_2)_nOC(O)OR^8$,
$(CH_2)_nOC(O)N(R^8)_2$,
$(CH_2)_nN(R^8)(R^8)$, and
$(CH_2)_nNR^8SO_2N(R^8)(R^8)$;
wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R^6; and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

Y is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_nC_{3-8}$ cycloalkyl,

$(CH_2)_n$aryl,
$(CH_2)_n$heterocyclyl, and
$(CH_2)_n$heteroaryl;

wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups selected from R^6; and alkyl, $(CH_2)_n$, cycloalkyl, and heterocyclyl are optionally substituted with one to three groups selected from R^6 and oxo;

R^1 is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CHR^7)_n$-C_{3-6} cycloalkyl,
$(CHR^7)_n$-$O(CHR^7)$aryl,
$(CHR^7)_n$aryl, and
$(CHR^7)_n$heteroaryl;

in which aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^6; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^2 is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_nC_{3-6}$ cycloalkyl, and
$(CH_2)_n$-aryl;

each R^3 is independently selected from
hydrogen,
C_{1-8} alkyl,
$(CH_2)_n$-aryl,
$(CH_2)_nC_{3-7}$ cycloalkyl,
$(CH_2)_n$-heteroaryl,
halo,
OR^7,
$NHSO_2R^7$,
$N(R^7)_2$,

C≡N,
CO_2R^7,
$C(R^7)(R^7)N(R^7)_2$,
NO_2,
$SO_2N(R^7)_2$,
$S(O)_mR^7$,
CF_3, and
OCF_3;

R^4 and R^5 are each independently selected from the group consisting of
hydrogen,
C_{1-10} alkyl, and
C_{3-8} cycloalkyl;
or R^4 and R^5 together with the nitrogen to which they are attached form a 5- to 8-membered ring optionally containing an additional heteroatom selected from O, S, and NR^7;
wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^6 is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_n$-aryl,
$(CH_2)_nC_{3-7}$ cycloalkyl,
$(CH_2)_n$-heteroaryl,
halo,
OR^7,
$NHSO_2R^7$,
$N(R^7)_2$,
C≡N,
CO_2R^7,
$C(R^7)(R^7)N(R^7)_2$,
NO_2,
$SO_2N(R^7)_2$,
$S(O)_mR^7$,

CF_3, and
OCF_3;

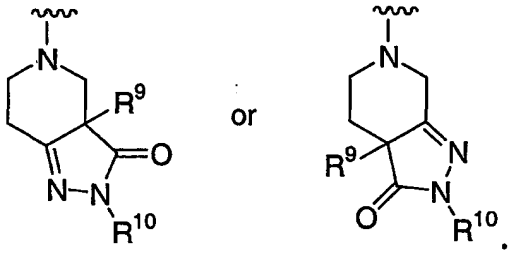
each R^7 is independently selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_n$-aryl, and
$(CH_2)_nC_{3-7}$ cycloalkyl;

each R^8 is independently selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
$(CH_2)_n$-aryl,
$(CH_2)_n$-heteroaryl, and
$(CH_2)_nC_{3-7}$ cycloalkyl;
wherein aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^6; and alkyl, cycloalkyl, and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo; or two R^8 groups together with the atoms to which they are attached form a 5- to 8-membered mono- or bi-cyclic ring system optionally containing an additional heteroatom selected from O, S, and NR^7;

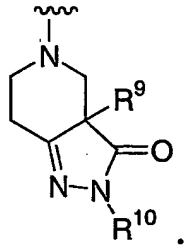
R^9 is selected from the group consisting of
C_{1-8} alkyl,
$(CH_2)_n$-C_{3-6} cycloalkyl,
$(CH_2)_n$heterocyclyl,
$(CH_2)_n$aryl, and
$(CH_2)_n$heteroaryl;
in which aryl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^6; and alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^{10} is C_{1-6} alkyl unsubstituted or substituted with one to three fluoro groups; and each R^{11} is independently hydrogen or C_{1-4} alkyl.

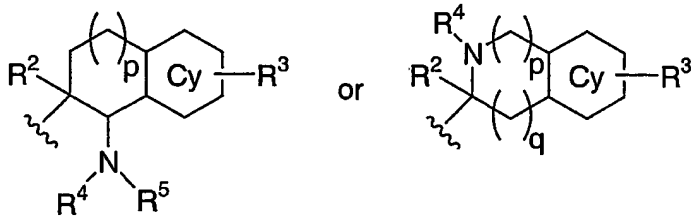
2. The compound of Claim 1 wherein Z is



3. The compound of Claim 2 wherein Z is



4. The compound of Claim 1 wherein Q is

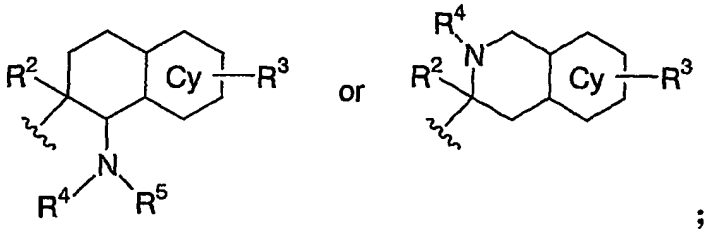


wherein

p is 1 or 2; and

q is 0 or 1.

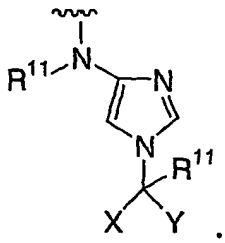
5. The compound of Claim 4 wherein Q is



;

and m = 0.

6. The compound of Claim 1 wherein Z is



.

7. The compound of Claim 6 wherein X is

$(CH_2)_n$-aryl,
$(CH_2)_n$-heteroaryl,
$(CH_2)_n$-heterocyclyl,
$(CH_2)_nC(O)N(R^8)(R^8)$,
$(CH_2)_nCO_2R^8$,
$(CH_2)_nOR^8$,
$(CH_2)_nNHC(O)R^8$, or
$(CH2)nNR^8SO_2R^8$;

wherein aryl and heteroaryl are optionally substituted with one to three groups selected from R^6; heterocyclyl is optionally substituted with one to three groups selected from R^6 and oxo; and the $(CH_2)_n$ group is optionally substituted with one to three groups selected from R^7, halo, $S(O)_mR^7$, $N(R^7)_2$, and OR^7;

and Y is
C_{1-8} alkyl,
$(CH_2)_nC_{5-7}$ cycloalkyl,
$(CH_2)_n$-aryl,
$(CH_2)_n$-heterocyclyl, or
$(CH_2)_n$-heteroaryl;
wherein aryl and heteroaryl are optionally substituted with one to three groups selected from R^6; and $(CH_2)_n$, alkyl, cycloalkyl, and heterocyclyl are optionally substituted with one to three groups selected from R^6 and oxo.

8. The compound of Claim 7 wherein Y is cyclohexyl, cycloheptyl, cyclopentyl, or C_{1-6} alkyl, each of which is unsubstituted or substituted with one to three groups selected from R^6 and oxo.

9. The compound of Claim 8 wherein each R^{11} is independently hydrogen or methyl and Y is cyclohexyl or C_{1-6} alkyl, wherein the cyclohexyl and alkyl groups are unsubstituted or substituted with one to three groups selected from R^6 and oxo.

10. The compound of Claim 1 wherein Cy is selected from the group consisting of benzene, pyridine, pyrazine, piperidine, and cyclohexane.

11. The compound of Claim 10 wherein Cy is benzene or cyclohexane.

12. The compound of Claim 1 wherein R^1 is $CH(R^7)$-aryl, $CH(R^7)$-heteroaryl, or $CH(R^7)OCH(R^7)$-aryl, wherein aryl and heteroaryl are unsubstituted or substituted with one or two R^6 groups.

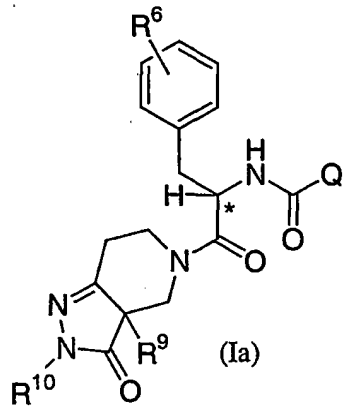
13. The compound of Claim 12 wherein R^1 is benzyl or benzyloxymethyl unsubstituted or substituted with one or two groups selected from halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, and OCF_3.

14. The compound of Claim 13 wherein R^1 is 4-chlorobenzyl, 4-fluorobenzyl, or 4-methoxybenzyl.

15. The compound of Claim 1 wherein R^2 is H or CH_3.

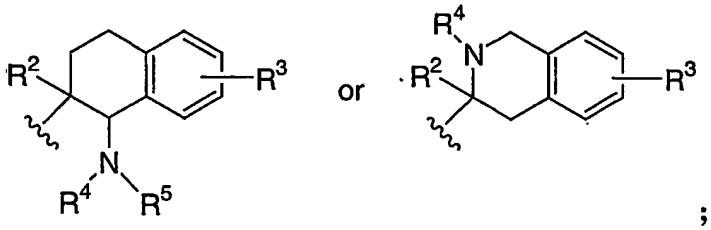
16. The compound of Claim 1 wherein the carbon atom marked with * has the *R* configuration.

17. The compound of Claim 5 of formula Ia:



(Ia)

wherein Q is



;

R^2 is hydrogen or methyl;

R^3 is as defined above;

R^4 and R^5 are each independently selected from the group consisting of

hydrogen,

C_{1-6} alkyl, and

C_{5-6} cycloalkyl;

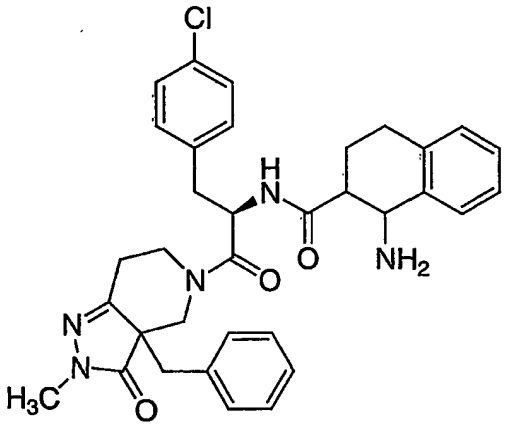
or R^4 and R^5 together with the nitrogen to which they are attached form a 5- to 7-membered ring optionally containing an additional heteroatom selected from O, S, and NR^7;
wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^6 and oxo;

R^6 is chloro, fluoro, CF_3, methoxy, or C_{1-4} alkyl;
R^7 is hydrogen, C_{1-8} alkyl, or C_{3-6} cycloalkyl;

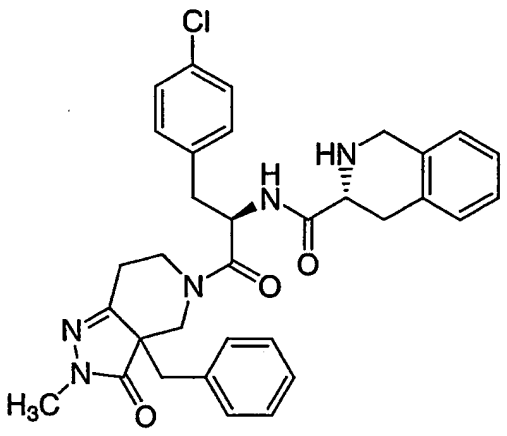
R^9 is phenyl, benzyl, pyridyl, or pyridylmethyl, each of which is unsubstituted or substituted with one or two R^6 groups; and
R^{10} is methyl or CH_2CF_3.

18. The compound of Claim 17 wherein the carbon atom marked with * has the *R* configuration.

19. The compound of Claim 18 which is



or



;

or a pharmaceutically aceptable salt thereof.

20. A method for the treatment or prevention of disorders, diseases or conditions responsive to the activation of the melanocortin receptor in a mammal in need thereof which comprises administering to the mammal a therapeutically effective amount of a compound according to Claim 1.

21. A method for the treatment or prevention of obesity in a mammal in need thereof which comprising administering to a mammal a therapeutically effective amount of a compound according to Claim 1.

22. A method for the treatment or prevention of diabetes mellitus in a mammal in need thereof comprising administering to a mammal a therapeutically effective amount of a compound according to Claim 1.

23. A method for the treatment or prevention of male or female sexual dysfunction in a mammal in need thereof comprising administering to a mammal a therapeutically effective amount of a compound according to Claim 1.

24. A method for the treatment or prevention of erectile dysfunction in a mammal in need thereof comprising administering to a mammal a therapeutically effective amount of a compound according to Claim 1.

25. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of Claim 25 further comprising a second active ingredient selected from the group consisting of an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α-glucosidase inhibitor, an HMG-CoA reductase inhibitor, a sequestrant cholesterol lowering agent, a β3 adrenergic receptor agonist, a neuropeptide Y antagonist, a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α_2-adrenergic receptor antagonist, and a dopamine receptor agonist.

27. A method of treating erectile dysfunction in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the composition of Claim 25.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/17014

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/437, 31/47, 31/4164 ; C07D 471/02, 401/12, 233/88

US CL :514/303, 307, 398 ; 546/120, 146 ; 548/326.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/303, 307, 398 ; 546/120, 146 ; 548/326.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 995 748 A (PFIZER PRODUCTS INC.) 26 April 2000 (26.04.00), examples 1-10 on pages 84-85.	1-27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 AUGUST 2001	Date of mailing of the international search report 25 SEP 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHANA A. LAKIN Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/17014

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/17014

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. The species are as follows:

I. Compounds of formula (I) where Z represents a bicyclic ring containing three N atoms as heteroatoms, pharmaceutical compositions containing these compounds and a method of using these compounds, classified in class 546.

II. Compounds of formula (I) where Z represents a 5-membered ring containing two N atoms as heteroatoms, pharmaceutical compositions containing these compounds and a method of using these compounds, classified in class 548.

The claims are deemed to correspond to the species listed above in the following manner:

Species I : Claims 2, 3 and 17-19

Species II : Claims 6-8

The following claims are generic: Claims 1, 4, 5, 9-16 and 20-27

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:
There is no common core which in the Markush Practice, is a significant structural element shared by all of the alternatives; see PCT Administrative Instructions Annex B Part I (f) (i) (B) (1).